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The Journal of
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Pregnancy in the Patient with Chronic Hypertension

BY

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THE following paper deals with 239 pregnancies in 222 patients who at the beginning of pregnancy already had chronic hypertension. Only patients who have been under our own care from before the 20th week of pregnancy till delivery have been included.

The cases belong to the second group in the following classification of the toxaemias of late pregnancy which is that in use in the Obstetric Unit, University College Hospital.

(1) *Pre-eclamptic toxaemia and eclampsia.* In this group are included all eclamptic patients and those with pre-eclamptic toxaemia, i.e., those patients who develop hypertension with or without albuminuria and oedema for the first time after the 20th week of pregnancy.

(2) *Hypertension in pregnancy.* We reserve this term for those patients who are known to have hypertension before the 20th week of pregnancy and in whom chronic glomerular nephritis is excluded.

(3) *Chronic glomerular nephritis* in pregnancy (often called nephritic toxaemia). In a previous paper[1] we have already reported on our experience of this group.

A large proportion of our cases of toxaemia of late pregnancy we are unable to classify since the patient has not been seen before the 20th week.

The standard of hypertension we adopt is a blood-pressure above 130/70. Either the systolic or diastolic pressure must be above that level, and neither must be below it. This high standard has been criticized on the ground that available statistics show that a fairly large proportion of women of child-bearing age, whether pregnant or not, have blood-pressures above that level. This, however, does not mean that such patients are normal. At least as large a proportion of young women have decayed teeth, but no one claims that decayed teeth are normal. If the lower standard of 140/90 were adopted many of our most instructive and interesting patients, who have had repeated unsuccessful pregnancies because of chronic hypertension, would have been excluded.

We find little in the literature relating to the behaviour of the hypertensive patient who becomes pregnant. This is chiefly because there is great confusion in classification. Most obstetricians still fail to differentiate between chronic hypertension and chronic glomerular nephritis, and even when the distinction is clearly recognized the patient who develops hypertension for the first time *after* the 20th week, without albuminuria, is often classified in the hypertensive group instead of, as in our classification, in the group pre-eclamptic toxaemia. We cannot stress too strongly that patients who start their pregnancy with the handicap of chronic hypertension, though that handicap is considerably less than that of the patient with chronic glomerular nephritis, constitute a distinct group, behave in a manner peculiar to themselves and require special care and study. One of the few papers clearly recognizing this group is that of Dill and his co-workers[2] which, however, deals only with the results of animal experiments. They produced chronic hypertension in rabbits by constricting the aorta, the following after-effects being noted in the subsequent pregnancies: (*a*) Repeated pregnancies had no noticeable effect on blood-pressure, albuminuria or histological renal changes; (*b*) the life expectancy seemed to be decreased—an impression only; (*c*) foetal resorption and death occurred in a large percentage, only 40 per cent of the animals giving birth to living foetûs. The cause of foetal death they

believed to be "anaemia of the uterus due to the severe vaso spasm giving rise to placental anaemia and infarction."

Wilson and Byrom[3] in their experimental work on "The Vicious Circle in Chronic Bright's Disease" found that of 5 rats which became pregnant after chronic hypertension had been produced by partial occlusion of one renal artery there was in all a marked fall in blood-pressure in the latter half of gestation, but it usually returned to its previous level after labour. They could not offer any explanation of the fall and were unable to say, from their observations, what was the effect if any of the pregnancy on the subsequent course of the hypertension.

Clinical History and Course

The patient may be a little older than usual. It is said that her bodily *habitus* is often peculiar in that she is short and stocky with a tendency to obesity but this is by no means constant and has not received any support from our investigation of height-weight ratios. Our impression is that there is usually a family history of hypertensive cardiovascular disease, and if blood relatives are examined it may be found that a higher proportion than usual of them are hypertensive even though still young. There may be a history of toxaemia or even eclampsia in a previous pregnancy, or of several unexplained miscarriages with inability to produce a living child.

The following is the usual course of events during the course of pregnancy. About or shortly after mid-pregnancy the blood-pressure begins to rise gradually. If and when it reaches 160/110, or thereabouts, albumin may appear in the urine and there may be oedema with lessened urinary output. When albumin has appeared in the urine it nearly always continues till after delivery, though it may not increase much or at all. In the more unfavourable cases other signs and symptoms of pre-eclamptic toxaemia may develop—headache, vomiting, disturbances of sight, antepartum haemorrhage, and there may even be eclampsia. The foetus may die *in utero* at any time in the course of the pregnancy, especially after the blood-pressure rises, but it is particularly apt to do so after albumin appears in the urine; or premature labour may occur with the birth of an infant that may or may not survive. The child, even when born alive, tends to be unusually small for the period of pregnancy. Thus at the end of the 36th week it may weigh no more than $3\frac{1}{2}$ to 4 pounds, no doubt due to the malnutrition following on the white infarc-

tion of the placenta so often present in these cases, as in chronic glomerular nephritis. This tendency to under-development must be taken into consideration when the question of premature termination of pregnancy arises. After delivery, the albumin usually disappears from the urine within a few weeks, the blood-pressure falls considerably, and may remain for several days at a low level. In a few weeks, however, when the patient resumes her normal activity it returns to its initial level, or thereabouts, and she seems to be little or no worse than before the pregnancy began. In a small percentage of cases, however, she becomes progressively worse after delivery and goes more or less quickly downhill, the blood-pressure is maintained at a very high level, perhaps 200/130 mm. or more, albuminuria persists and she dies in from 2 to 6 years of cerebral haemorrhage, cardiac failure or rarely from uraemia. These are generally patients whose condition at the start of pregnancy was bad with blood-pressure in the region of 180 mm. or more. It is possible that they are examples of malignant hypertension, and that apart altogether from a complicating pregnancy they had a short expectation of life. Whether the disease progresses more rapidly during and after the pregnancy is not easy to determine though the probability that it often does so is very great.

Family history of hypertension. We have said above that we had an impression that a family history of hypertension and deaths from cardiovascular disease was more frequent in pregnant women with chronic hypertension than in normal pregnant women. This impression has not, however, received any support from our records, for of 217 hypertensive patients in the present series whose family history had been noted when they first came to the clinic there was a positive history in 33 (15.1 per cent). We compared this with that of 100 consecutive normal pregnant women in 16 of whom there was a positive history. The information had only been obtained by questioning the patient at the time of booking in. This was done by a nursing sister. Relatives were not seen or examined.

Age. The average age of the 222 hypertensive patients was 31.02 years, whereas the average age of 500 consecutive patients (not hypertensives) was 28.4 years.

Weight-height ratio. This was obtained by dividing weight in pounds by height in inches. The greater the weight in proportion to height, therefore, the larger the quotient or weight-height ratio ($\frac{W}{H}$) should be. We have already seen that there is a general belief that patients with chronic hypertension are of

more stocky build than those who have normal blood-pressures. This has received little or no support from our investigation for of 133 of our hypertensive patients in whom the weight and height were recorded at the first examination the ratio was 2.09. In 100 normal (non-hypertensive) pregnant women it was 1.90.

Previous history of toxaemia. One hundred and ten women had had one or more pregnancies when they first came under observation. Of these 38 were known to have had toxaemia of pregnancy including 9 who had eclampsia; 5 others had had antepartum haemorrhage. Nine (7 per cent) of the others who had been under observation in the previous pregnancies were known to have then been normal. In the remainder (58) the history of the previous pregnancies was not sufficiently known to enable us to judge whether toxaemia was present or not. Presumably its incidence was very high as the percentage of dead births, abortions and terminations, before viability was high (40 per cent).

History of previous kidney disease. Of the 222 patients only 3 gave a history of previous kidney disease. One had had pyelitis 20 years previously, one had a left nephrectomy a year previously for tuberculosis, and one gave an indefinite history of "kidney trouble."

Pyelitis as a complication of hypertension. In 40 of the patients who had albuminuria during pregnancy under observation the urine was examined microscopically. Pus was found in only 2 cases. We may, therefore, assume that there were not more than 2 patients who had pyelitis in the hypertensive pregnancy.

Results of previous pregnancies. There were 252 pregnancies which had occurred prior to the one in which the patients first came under our observation. These were in 110 patients. The foetal salvage (i.e. those cases in which the child left hospital alive and well) was 160 (63.5 per cent). There were 88 abortions, spontaneous or induced, macerated foetûs and neonatal deaths from prematurity (34.9 per cent) in addition to 4 dead or stillbirths due to obstetric causes (1.5 per cent).

Degree of initial hypertension. Of the 239 pregnancies there were 95 in which the systolic blood-pressure at the start of pregnancy was between 130 and 140 (40 per cent); 92 in which it was between 140 and 150 (38.4 per cent) and 52 in which it was 150 or over (21.7 per cent). Of the last group the initial blood-pressure was 160 or over in 31. The blood-pressure is taken after rest by the auditory method and an initial high reading

if not maintained at subsequent visits is ignored; patients showing this are not included in the series.

Parity. The parity of the patients in the 239 pregnancies under our observation is shown in Table I.

TABLE I.

Parity	0	1	2	3	4	5	6	7	8	9	10	11	Total
No. of patients	112	57	36	15	5	6	2	1	2	1	1	1	239

Exacerbation of the disease during the pregnancy. Of the 239 pregnancies there were 5 in which it could not be determined whether exacerbation during the pregnancy had occurred or not. Of the remaining 234 exacerbation characterized by rise of blood-pressure and albuminuria with or without oedema (but generally with well-marked oedema), and sometimes with other signs of pre-eclamptic toxaemia—vomiting, headaches, visual disturbances —occurred in 42 (17.9 per cent). Rise of blood-pressure alone without albuminuria but sometimes with considerable clinical oedema was the only evidence of exacerbation in 143 (61.1 per cent). Included in these two groups there were 6 cases of ante-partum haemorrhage, 4 in which there were serious changes in the fundi oculi detailed later, one of bilateral cortical necrosis of the kidneys, 2 of eclampsia and one of congestive cardiac failure with pleural effusion. In 10 cases the pregnancy terminated early, before exacerbation had time to occur, 3 spontaneously and 7 artificially. All these 7 were cases in which the disease was very serious and in which it was considered unwise to allow the pregnancy to proceed. If we count these 7 cases we find that exacerbation occurred in 192 (82 per cent). In 39 (17 per cent) there was no exacerbation.

Time of exacerbation. Most of the exacerbations occurred after the 30th week and it was rare before the 26th week. The frequency distribution is shown in the following table:

TABLE II.

Showing Time of Occurrence of Exacerbation with Albuminuria in Forty Hypertensive Patients.

Weeks	15 to 20	21 to 25	26 to 30	31 to 35	36 to 40
No. of patients	1	2	3	15	19

Time of appearance of albuminuria in relation to blood-pressure. Corwin and Herrick[4] state that when the blood-pressure in the pregnant patient with chronic hypertension reaches 180 mm. Hg albumin rather abruptly appears in the urine. This was noted in 41 cases of the present series. The mean was 154/98 but it varied between 130/92 and 215/140. Little really accurate information can, however, be gained from the records as the blood-pressure in these hypertensive patients is extremely variable, and changes from hour to hour, and though the pressure may be relatively low when the albuminuria is first discovered it may have been much higher when it appeared. It is of interest, however, to note that there were 5 cases in which the blood-pressure was 170/110, 180/100, 180/110, 190/100 and 190/115 without there being any albumin in the urine. The initial pressures in these patients were 136/80, 152/90, 160/90, 150/108 and 138/74 respectively. More accurate information is to be gained from the study of two patients who were in hospital during most of their pregnancies with daily urine and blood-pressure examinations. Albumin appeared in one when the blood-pressure was 168/118 and in the other at 150/82. The initial blood-pressures in them were 142/84 and 140/90 respectively. These results should be considered in conjunction with the experiments of Chesley[5] *et al.* who by immersing the hand in ice water to cause a sudden vascular constriction invariably produced albuminuria when the systolic pressures rose 16 mm. or more.

The question of "occult nephritis." It might be questioned whether the patients who 'broke down' in the course of their pregnancy developing albuminuria and raised blood-pressure with or without their accompaniments, oedema and antepartum haemorrhage, were fundamentally different in nature from those patients in whom exacerbation did not occur or in whom the only evidence of exacerbation was a rise in blood-pressure. Are the patients who 'break down' really examples of the so-called occult or subliminal or latent nephritis claimed by Kellogg[6] and by Gibberd[7] to be a cause of "recurrent toxaemia"? We were prejudiced in favour of this view, because of the results of our own experimental work published in 1930.[8] We produced chronic renal damage, characterized histologically by interstitial change and cystic dilatation of the convoluted tubules, by injecting sodium oxalate or uranium nitrate, and observed the animals between and during subsequent pregnancies. It was found (1) that chronic renal damage might exist between preg-

nancies without giving any clinical indication of its presence; (2) that in those patients, the subjects of "occult nephritis," exacerbation in the form of albuminuria appeared towards the end of pregnancy. This question has been often considered by us in the course of these observations, and though it cannot be finally decided until material for histological investigation of the kidneys is available, we believe that the evidence so far at hand does not support the assumption that there is a latent nephritis underlying the exacerbation, and that for the following reasons: (*a*) We have observed a number of these patients for several years, some as long as 10 or 12, and in no case have we observed the latent nephritis become manifest. As chronic glomerular nephritis is a progressive disease, persistent albuminuria and other signs of kidney disease might be expected to appear fairly soon, and especially after, and perhaps as a result of, repeated pregnancies. (*b*) These patients in successive pregnancies do not always behave in the same way. In one pregnancy they may undergo exacerbation with albuminuria and in those immediately preceding and succeeding they may not. For example, one patient (D1122) in her second pregnancy exacerbated at 18 weeks with rise of blood-pressure, albuminuria and antepartum haemorrhage, so that labour had to be induced at the 28th week. In the next pregnancy the blood-pressure at the 9th week was 150/90. It did not rise any higher, there was no albuminuria or oedema and a live child, weighing 7 pounds, was born by Caesarean section at the 38th week. In another (A955) the blood-pressure early in her first pregnancy was 150/90. It rose to 168/104 with albuminuria and oedema of hands and both legs. In the next pregnancy 2 years later though the initial blood-pressure was 150/82 and it rose to 178/100 there was no albuminuria but only a slight oedema of the legs. (*c*) It is well known that in chronic glomerular nephritis the blood-pressure is low as compared with that of the patient who has chronic hypertension. If those patients who later on in pregnancy developed albuminuria were examples of latent chronic glomerular nephritis we would expect the initial blood-pressure to be significantly lower than that of those patients in whom there was no exacerbation or in whom the sole evidence of it was a further rise of blood-pressure. We find, however, that the mean blood-pressure among the patients who developed albuminuria was 151/90 with a range as high as 190/140 and that in the patients who did not develop albuminuria the mean was 145/74 with a highest range of 160/100. (*d*) Hypertensive patients under obser-

vation in hospital throughout practically the entire pregnancy did not show any albuminuria prior to the sudden exacerbation though the urine was tested daily. This was especially noticeable in D1108 and E730, who after repeated unsuccessful pregnancies were during their next pregnancy kept in hospital. In both cases exacerbation took place at 33 and 29 weeks respectively with rise of blood-pressure, albuminuria and oedema. Albumin was consistently absent from the urine before those times as it has been since a few weeks following delivery. In one of these patients (D1108) the chronic hypertension followed eclampsia in the first pregnancy and so far histological evidence has not been produced that chronic glomerular nephritis is a result of that disease.

Influence of age on exacerbation. The age of the patient seemed to have a decided influence in determining whether exacerbation would occur or not. Among the patients aged 30 or over the exacerbation rate (counting as exacerbation the appearance of albuminuria) was 25.6 per cent. Among the patients under 30 it was 14.3 per cent.

Method of terminating pregnancy. This was as follows. In 211 labour came on spontaneously. Caesarean section was carried out on 8, curettage on one, bag induction with or without artificial rupture of membranes in 4, artificial rupture of membranes alone in one, abdominal hysterotomy in 4, bougie induction in 3 and in 7 induction by medicinal means.

Duration of pregnancy in those ending spontaneously. This is shown in the following table:

TABLE III.

Showing Duration of Pregnancy in 211 Cases Ending Spontaneously.

Week	Term	38	37	36	35	34	32	30	28	21	15	12
No. of cases	176	5	7	5	4	2	3	2	3	1	2	1

Pregnancy, therefore, failed to go to term in 35 cases (16.5 per cent.

Foetal and neonatal mortality. In the 239 pregnancies there were 39 which ended in dead births, abortions (including induced abortions and hysterotomies) or neonatal deaths (16.2 per cent). The foetal salvage, therefore, was 83.8 per cent. Included in the dead births there were 13 macerated foetûs from 13 preg-

nancies. In 5 of these pregnancies there was no albuminuria at any time; in 2 there was antepartum haemorrhage together with hypertension but in the remaining 3 there was hypertension alone —the highest recorded being 164/80, 190/115 and 180/110. There were 5 spontaneous abortions in the series after the patient came under observation, in 3 of which there was albuminuria and hypertension, while 2 had hypertension but no albuminuria. There were 4 neonatal deaths after spontaneous delivery; in all the infants had been premature and undersized. In 3 of the 4 there had been albuminuria as well as hypertension and in one of these there had also been antepartum haemorrhage. In the fourth patient there had been no albuminuria but only hypertension. It may be concluded, therefore, that while intra-uterine death of the foetus is usually preceded by albuminuria in addition to hypertension it may occur in absence of albuminuria, especially if the blood-pressure is very high—160 mm. or over. The same applies to spontaneous abortion and premature labour.

Relation of initial blood-pressure to the prospect of successful pregnancy. There were 25 cases in which the initial blood-pressure was 150/100 or over. A study of these cases indicates that if a patient starts her pregnancy with a blood-pressure at this level she is unlikely to have a successful pregnancy. From the 25 pregnancies there were only 8 infants that survived (32 per cent). One patient with an initial blood-pressure of 176/114 produced a live child at term but the mother died a year later. No woman with an initial blood-pressure of 180 mm. or over bore a live child. Diastolic pressure alone seemed to be an equally reliable guide to prognosis. There were 19 patients in the series who had an initial diastolic pressure of 100 or over and only 6 (31.5 per cent) of these produced a child that survived.

Renal Function Tests in relation to Prognosis.

In our experience these have been of little value in prognosis. The following routine estimations were made on the blood: urea, non-protein nitrogen, uric acid, calcium, chlorides and cholestrol, and also the urea clearance and urea concentration. Only those cases have been included in this analysis in which the biochemical tests were made early in pregnancy and before exacerbation. There were 35 of these initial tests, and usually the clinical condition of the patient was serious enough to warrant admission when she first came under observation. In some the admission was due to the fact that there had been several unsuccessful pregnancies and it was, therefore, judged that the

patient required special institutional care. In general, therefore, they included the worst cases.

Blood urea. It is well established that in normal pregnancy the blood urea is considerably lower than in non-pregnant woman and that a figure of 20 mgm. per cent or over is unusual. We might, therefore, be justified in regarding a blood urea of 30 or over as indicating deficient renal function with a correspondingly bad prognosis for the success of the pregnancy. There were only 5 pregnancies in which the initial blood urea was 30 or over and only 2 of these ended in the birth of living and viable infants (40 per cent). This should be compared with the salvage of 83.8 per cent in the whole series. If we take 25 mgm. per cent as the borderline figure there were 18 pregnancies in which the blood urea was 25 or over. The foetal salvage was 66.6 per cent. Of the 17 in which the blood urea was under 25 the salvage was 64.7 per cent. There was, therefore, no significant difference between them. Did a high initial blood urea indicate that exacerbation was more likely to occur? The answer is "no," for of the 18 pregnancies in which it was above 25 albuminuria occurred in 8 (44.4 per cent), whereas of the 17 pregnancies in which it was below 25 albuminuria occurred in 7 (46.6 per cent). Of the 5 patients with an initial blood urea of 30 or over only 2 developed albuminuria; in one the initial blood urea was 48, in the other 32. Another patient with an initial blood urea of 34 did not develop albuminuria though a macerated foetus was born. Of the 30 pregnancies in which the initial blood urea was under 30 albuminuria developed in 13 (43.3 per cent). It may, therefore, be said that the outlook for the foetus is much worse if the blood urea at the start of pregnancy is 30 mgm. per cent or over but that the initial level of blood urea seemed to make no difference as to whether albuminuria would develop or not. The figures are small and cannot, therefore, be regarded as conclusive. Further study is needed.

Urea concentration test. (Maclean and de Wesselow.) This did not seem to be of any value in prognosis. Taking 2.5 gms. per cent as the border line there were 25 cases in which the initial urea concentration was above this level. The foetal salvage was 17 (68 per cent), albuminuria subsequently occurred in 13, and there were 2 patients in whom the pregnancy terminated early before exacerbation could occur—say 50 per cent in all. There were 7 cases in which the urea concentration was under 2.5. The foetal salvage was 5 (71.4 per cent) and albumin appeared in the urine in one (14.3 per cent).

Urea clearance test (Van Slyke). This also did not seem to be of any value from the point of view of prognosis. Taking 60 as the border line between good and bad renal function there were 6 below this. The foetal salvage was 83.3 per cent. There were 23 above with a foetal salvage of 73.9 per cent. Nor was it of any value as indicating the later onset of albuminuria for this occurred with equal frequency in the above two groups.

Blood uric acid. This too seemed to be of no value in relation to prognosis. There were 14 patients with an initial uric acid of 3.0 mgm. per cent or over. The foetal salvage was 64 per cent; there were 18 patients with an initial uric acid below 3; 12 live infants were obtained (66.6 per cent). Also 2 of the mothers with this low initial blood uric acid have died both within 6 years after delivery. From the study of blood calcium, chlorides and cholestrol nothing of value was obtained.

Fundal Changes.

Records of fundal examinations by the staff of the Eye Department of the hospital are available in 51 patients. Of these 44 were normal, 3 had retinal arterio-sclerosis only, 2 had arterio-sclerosis combined with haemorrhages and exudates, one had bilateral papilloedema, and one retinal arterio-sclerosis, haemorrhages, exudates and papilloedema. The patient with papilloedema died within a year at home. Her highest blood-pressure during pregnancy was 290/140. Of the 2 patients with haemorrhages and exudates one died 4 months after delivery, the other was seriously ill 9 months later but has since been lost sight of. Of the patients with retinal arterio-sclerosis only, one was alive and in fair condition 9 years later, the second was in a mental asylum, also 9 years later, and the third was alive and in fair condition 10 years after delivery. One of the patients whose fundus was normal had had albuminuric retinitis in a toxaemic pregnancy 2 years before. The patient with haemorrhage, exudates, arterio-sclerosis and papilloedema died during labour of congestive heart failure. Her blood-pressure at 26 weeks (the highest reached) was 230/140.

Prognosis for the Mother

Immediate: Of the 222 mothers 2 died at delivery or in the puerperium, one of congestive heart failure on the day of delivery, the other of bilateral cortical necrosis in the puerperium. *Remote*: Four others are known to be dead but as in the great

majority a prolonged follow-up was not obtained this cannot be regarded as the total death rate in these cases. A far truer indication of the remote prognosis is the ascertained death rate in the smaller series of 86 pregnancies in 65 patients followed up for periods up to 12 years published by us in 1938[8] from which we take the following quotation . . . " Judged by the general condition, height of blood-pressure and cardiac changes the pregnancy did not seem to have any ill effect in 52 of the 65 patients. In 7 the effect of the pregnancy was unknown as the condition before pregnancy was unknown; 6 are dead (9.2 per cent) . . . In spite of these 6 fatal cases we believe that the large majority of patients with simple hypertension may pass even through several pregnancies, go to term and give birth to live infants without suffering any demonstrable deterioration in their condition. We could give many examples in support of this contention from the cases in the series. One of them, Mrs. D. 535/30, we have observed in 5 pregnancies and in the intervals between, during the years from 1929 to 1939; all the pregnancies have gone to term except one that ended at 36 weeks in the birth of a macerated foetus. In 1929, before the first observed pregnancy began, her blood-pressure was 160/100, albumin nil. Now, 10 years later, it is not any higher, the urine is free from albumin, and the general condition seems as good as in 1929. In the last pregnancy (1938-9) the blood urea was 16, urea concentration 2.65, urea clearance 43, highest blood-pressure 160/80, albumin nil, blood-pressure on discharge 108/56. In this respect our detailed study of cases for this report has only served to confirm the general impression we have obtained from watching these patients in the hospital wards for a number of years." In Table IV we give essential details of the 6 patients of the present series who are known to be dead.

Treatment

In patients with very severe hypertension, certainly in those over 160/100 at the start of pregnancy, the question of terminating pregnancy will have to be considered. We have already seen that the chance of a successful pregnancy followed by the birth of a living and viable child is comparatively small when the initial blood-pressure is 150/100 or over, and this fact may weigh heavily in the decision. In the rare cases in which the initial blood-pressure of the patient is 180 or over with albuminuria and still more if the blood urea is 40 mgm. per cent or over with or without serious fundal changes pregnancy should be ter-

TABLE IV

SHOWING PARTICULARS OF FATAL CASES.

Number	Age	Parity	Initial B.P.	Highest B.P.	Initial blood urea	Fundal changes	Other signs of exacerbation	Duration of pregnancy	Mode of termination	Result to Foetus	Time of death
1020/31	23	1	290/140	do. (slight cardiac enlargement)	22 (slight cardiac enlargement)	Bilateral papilloedema	None allowed	14 weeks	Hysterectomy	D	2 months later
655/31	34	2	176/114	280/150	21	Retinal exudates and haemorrhages	Alb. solid Eclampsia	40 weeks	Spont.	A	20 months later
960/29	31	2	210/110	240/132	28	Arterio-sclerosis Exudates and haemorrhages	Albuminuria	6 weeks	Induced abortion	D	4 months later
1101/29	33	1	P.M. diagnosis arterio-sclerotic kidney found.	230/150	30 (not initial)	Exudates	Concealed accidental hge. Alb. solid cortical necrosis of kidney	21 weeks	Spont.	D	Puerperium
639/33	38	2	160/100	160/100	21	—	—	15 weeks	Spont.	D	Died in asylum some yrs. later
B.797	40	8	P.M. diagnosis	230/140 at 26 weeks	Normal 10 days before death	Arterio-sclerosis, haemorrhages, exudates, papilloedema	Congestive heart failure, pleural effusion, oedema, albuminuria	38 weeks	Spont.	A	Day of delivery

minated forthwith. This should certainly be done if there is papilloedema which invariably indicates malignant hypertension even in the absence of albuminuria or of evidence of impaired renal function.

If, as is generally the case, it is decided to allow the pregnancy to proceed, supervision should be careful and practically continuous. Patients who have already had one or more unsuccessful pregnancies and who have not succeeded in bearing a living and viable child are best kept under constant observation in hospital where they can be as free as possible from domestic duties and worries, and be kept in bed, preferably in conditions where they can secure the maximum amount of fresh air and sunshine, if and when the blood-pressure shows a tendency to rise to a dangerous level. Diet is probably less important than rest but butcher meat and soups made from it are best cut down to a minimum or avoided altogether. Meals should be largely vegetarian with a high carbohydrate content, and should include plenty of fresh green stuff and fruit, 2 pints of milk and not more than one egg daily but without beans, peas or lentils. To ensure an adequate supply of important vitamins, 2 halibut liver oil capsules should be given daily and Bemax or Marmite. If sleeplessness is troublesome a mild sedative such as a small dose of bromide and chloral should be given at night, and tea and coffee should be prohibited after 5 p.m. The use of progestin has been advised to control the blood-pressure and good results have been claimed by Robson and Paterson.[10] We have used it in several cases in doses of 5 milligrams daily but apparently without any benefit. Ultra violet light is possibly of value though convincing evidence of benefit from its use is difficult to obtain. If there is albuminuria, however, it is our opinion that it does more harm than good as the albumin seems to increase as a result of its use.

When the foetus has reached the stage of viability, i.e. at the end of the 36th week, the question of terminating pregnancy must be considered and in this we are largely guided by whether or not there has been exacerbation either in the form of a serious rise in blood-pressure or albuminuria. If this occurs and does not improve with rest in bed it may be thought unwise to allow the pregnancy to continue further on account of the risk of intrauterine death. Against this must be weighed the possibility of delivering a premature undersized and puny child that may not survive. To minimize this risk all the clinical methods available to us—height of fundus, abdominal girth, clinical estimation of the size and ossification of the head examined by abdominal and

vaginal palpation and X-ray cephalometry—of assessing the size and weight of the foetus should be used. It is generally unwise to terminate pregnancy for the sake of the child unless the foetus weighs at least 4 pounds. When the birth of a live child is very important, as for example when there have been several unsuccessful pregnancies and no living child, we believe that Caesarean section offers the best chance to the baby, for the head of the premature infant is apt to stand even easy labour badly. A degree of cerebral haemorrhage, often taking the form of clots in the ventricles, that is incompatible with survival occurs seemingly without any cause, and in the most unexpected circumstances. In the full-time infant the plasma prothrombin level averages between 14 and 39 per cent of that of the normal adult but in the premature infant it is only 11 per cent (Hellman and Shettles[11]). This no doubt predisposes the premature infant to fatal haemorrhage into vital organs. Vitamin K should therefore be administered to the mother during the last month of pregnancy and if possible 4 to 5 hours before delivery. It goes without saying that if delivery *per vias naturales* is allowed the forceps should not be used and the membranes should be preserved intact as long as possible. This means that premature induction by means of rupture of the membranes is ruled out. The best method is the solid rubber bougie. Later the question of allowing further pregnancies will arise, and while it is probably true that many hypertensive patients are little the worse even after several full-time pregnancies one can never be sure of this; and in any case it is undesirable that the hypertensive patient should be burdened with the care of a numerous family. If there has been albumin in the urine as a result of an exacerbation of the hypertensive condition it usually clears up in a few weeks but it may take as long as 1½ or 2 years. Another pregnancy should not be allowed till this has occurred.

Summary

1. The paper deals with 239 pregnancies in 222 patients who already had chronic hypertension when pregnancy began.

2. Exacerbation in the form of albuminuria, oedema, etc., occurred in 17.9 per cent of the 239 pregnancies. If a further rise in blood-pressure alone or with oedema were taken as evidence of exacerbation this occurred in 82 per cent. In 17 per cent of the cases there was no exacerbation of any kind.

3. We did not find any evidence that the patients in whom exacerbation occurred with the appearance of albumin in the

urine, oedema and other signs of pre-eclamptic toxaemia were suffering from occult or latent nephritis or that the underlying disease in them was fundamentally different from that in those who did not undergo exacerbation, or in whom its only evidence was a further rise in blood-pressure. The evidence for this view is discussed.

4. Exacerbation seemed to be more likely to occur in patients of 30 years of age or over than in those under 30.

5. The foetal and neonatal mortality was 16.2 per cent. While intra-uterine death of the foetus was usually preceded by albuminuria it also occurred in absence of albuminuria, especially if the blood-pressure rose to 160 mm. or over. The same applied to spontaneous abortion and premature labour.

6. If a patient started her pregnancy with a blood-pressure of 150/100 or over there was little likelihood (32 per cent) of a successful pregnancy with the birth of a living and viable child. Diastolic pressure alone seemed to be an equally reliable guide to prognosis. If the initial diastolic pressure was 100 or over the chances for a successful pregnancy were poor (31.5 per cent).

7. Tests of renal function were of little help in prognosis. The most valuable seemed to be the blood urea. If this was 30 mgm. per cent or over at the start of pregnancy the chance of a living and viable child was small.

8. The clinical course, prognosis and treatment are discussed.

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A Clinical and Pathological Study of the Permanently Enlarged Uterus

BY

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IT IS our purpose to endeavour to segregate certain uterine diseases which are now confusedly grouped; to endeavour to expound the pathology underlying each of these clinical entities; to state or to speculate upon the causative agents which motivate these pathological changes, and lastly, to try to outline a comprehensive and logical therapeutic approach to each of these clinical groups.

One frequently hears of a clinical diagnosis of enlarged uterus, but how many of us try to visualize the disease processes which have brought about this change? If, perchance, we speak of an enlargement of the liver, we at once automatically begin to speculate as to the disease which has caused such a change in such an important organ, and we are not satisfied until we have found a satisfactory answer to our self-imposed questions. But this is not true of an enlargement of the uterus. How many of us visualize that symmetrical and asymmetrical enlargements are purely the differences between a general uterine response to a general cause, and an exaggerated local response to a similar cause, respectively? For we wish to emphasize that fibroids, which are the commonest cause of asymmetry, are but the exaggerated local expression of a general cause that affects the uterus and pelvic organs generally. How many of us try to visualize the uterine changes incidental to uterine endometriosis, when we are confronted with an enlargement of the uterus which may be either symmetrical or asymmetrical? And how many of us have speculated upon the probable common underlying causative agents in all these diseases?

After careful study of the clinical findings and pathological processes in diseases which cause symmetrical and asymmetrical enlargement of the uterus, we have arrived at a classification which we think rational and is based upon facts—a classification

which gives one a very comprehensive view of the whole subject of benign uterine enlargements. It would take us too far afield to deal with the malignant diseases of the uterus, so our description will be restricted to the benign types of uterine disease.

Permanent Uterine Enlargements

Permanent uterine enlargements of the uterus are classified into: 1. Infections. 2. Endocrine imbalances.

Now this classification is based upon the causative motivating agents. But it may be contended, and with justice, that this is an unwarranted assumption. The only answer we can give to such a contention is that the weight of evidence is overwhelmingly great, and if we wait until all the facts are mathematically correct, we will wait in vain. Let us not forget that wisdom consists in drawing correct conclusions from inconclusive evidence.

1. *Enlargement of the Uterus due to Infection.*

The common uterine disease due to an infection is that very frequent condition, the so-called chronic metritis. This disease has had a varied nomenclature in the literature, such as among others chronic metritis, chronic arterio-sclerotic uterus, fibrosis uteri, and haemorrhagia metropathica. Its name ought to be chronic subinvolution, because, as pointed out by Goodall, it can arise only out of the sequelae of an infected abortion or labour at term. In studies from the Royal Victoria Hospital,[1] Goodall showed that the parturient uterus, immediately after birth, weighs approximately 1,000 grammes, whereas the same organ, in its original state, weighs between 60 and 75 grammes. So in its involution, the uterus has to liquefy approximately 900 grammes of superfluous uterine tissue. It was also demonstrated that not all the component tissues of the uterus are equally susceptible to the katalytic influence which destroys these redundant tissues. The more highly specialized muscle-cells of the uterus succumb much more readily than do the connective tissue elements—the fibrous and elastic tissues. These are resistant in the order mentioned, the elastic elements being particularly refractory to the katalysis. Goodall also pointed out that the katalysis must proceed at a definite rate and with a definite force, otherwise destruction will be only partial, and the tissues will remain in a state of incomplete katalysis, leaving the uterus permanently surcharged with dead or inactivated remnants. These redundancies become permanent, ineffaceable traces of a

former pregnancy. Ineffaceable—except by the sequence of another pregnancy followed by a very normal complete involution. Goodall's work demonstrated that in 384 uteri of parous women, traces of redundancies were found in all but one, a vigorous woman of 20 years, who had borne a child one year previously and had died an accidental death. Autopsy showed the organs of the body to be in an exceptionally normal state.

From this we gather that the return to complete normalcy is a rare exception, and that by inference, more than 99 per cent of women, owing to our present mode of living, have already, at the time of their first pregnancy, some incipient metabolic derangement which prevents a complete return of the uterus to its pristine non-pregnant state. Given this first premise, the second statement naturally becomes a corollary to it. And that is, that these remnants grew more abundant as age and multiparity increased. This katalysis, to be complete, implies a liquefaction of these tissues to permit of their absorption. Any arrest in the rate of involution causes a partial block upon the involution processes, and permits a crystallization of tissue in the state in which the block finds it. The block may be partial or complete, depending upon the strength and duration of the agent which is at work. For example, any very acute disease, such as lobar pneumonia, which brings all the body's defensive measures into play and overwhelms the body with its toxicity, will put a complete block upon the parturient uterus, and involution will be resumed only after recovery from pneumonia. But the common uterine infections of the puerperium, and after abortions, are chiefly local, with very insignificant corporeal reactions. Yet these are the very infections which, by their lack of acuteness and lack of general reaction to create a complete immunity, become chronic and lasting, and place a reduced rate upon, and produce an incompleteness of, involution. This leaves the organ surcharged with products which it should have destroyed to the degree to permit absorption. In this surcharged organ there will be a preponderance of elastic and fibrous tissues at the expense of the muscle and this observation has led to the name of fibrosis uteri. Since the chief redundancies of elastica are in the immediate vicinity of the blood-vessels, the misnomer of arterio-sclerotic uterus was a natural, but mistaken, sequence.

What are the clinical and pathological facts of chronic subinvolution? First, it is a sequence, and a sequence only of an abnormal post-conceptual involution. Chronic subin-

volution cannot occur except as a result of a faulty involution following conception. This is a *sine qua non*. There are incidental combinations which will be dealt with later, which resemble subinvolution, but are readily distinguishable. Second, when a uterus in a state of involution becomes infected, there develops a slowing-down in the processes of involution. This is called a block. Clinically it is diagnosed by the fundus being higher than normal for the number of days which have elapsed since delivery. On palpation the uterus is large and softish, and the cervix is usually equally retarded in its involution, though this is less easily appreciated, for the reason that cervical involution is poorly understood, much less understood than uterine involution. It is less dramatic and, therefore, less attractive as a subject of research. After a period of months the uterus remains enlarged and has gradually changed into a hard, globular, and often sensitive symmetrical organ. Crystallization of its tissues has occurred. The condition is now permanent.

The new concept and pathology of this condition was outlined by Goodall in a previous paper published in the *Journal of Obstetrics and Gynaecology of the British Empire*, under the title of "Gynaecological and Puerperal Thrombophlebitis Contrasted with Phlegmasia Alba Dolens."[2] A short résumé of this is necessary here, to maintain sequence. Chronic subinvolution in its initial stages undergoes the changes described above. It implies a puerperal uterus in addition to a low-grade tenacious infection. The final pathological findings of cases of chronic subinvolution are so uniform that it bespeaks a specific causative agent. It is not to be inferred that the infective agent is a specific organism, but we wish to convey the idea that, apart from morphology, microbic specificity, in the majority of instances, lies in a constancy of degree of virulence and tenacity, and the final establishment of partial or complete symbiosis with the host. The essential feature of these infections, which lead to chronic subinvolution, is that they produce a low-grade lymphatic block, not only of the lymphatic vessels, but of the intercellular lymph spaces. The parallel between these infections and those of thrombophlebitis is very close indeed. The resultant is a filling of the lymph channels with a proliferated endothelial overgrowth, and a block in the normal flow of the lymph and consequent lymph stasis. Whether there is a progressive fibrosis due to the infection and abnormal lymph stasis has never been proved. Nor has this point been proven in cases of phlegmasia of the leg, where the structures are more exposed

to close observation. But phlegmasia of the leg does demonstrate one thing, that is, the permanency of the deformity if it is not quickly resolved. The extent and degree and duration of this determine the degree of arrest of the involution process and the consequent degree of chronic subinvolution. In the majority of instances the infection is limited to the uterine wall, but it may extend into the parametrial tissues and eventually reach the legs, and even metastasize in remote parts of the body. But, we repeat, in the vast majority of cases the disease is restricted to the uterus. The cervix, having hypertrophied under the influence of the pregnancy hormones, and having been traumatized by the labour or abortion, is usually infected with the same strain, and undergoes the same arrest of its involution, and manifests the same lymph block, so that this parallel involvement of both cervix and uterus is an invaluable aid to the diagnosis. If the easily accessible cervix is found to be enlarged, hard and cystic, in a word, if it is the seat of a chronic cervicitis (not endocervicitis), it is a fair inference that the superimposed uterus is in a similar state of chronic subinvolution. In 90 per cent of cases that inference is borne out.

The more minute details of the pathology will be found in the article quoted above. What are the symptoms of this disease? There has been so much misunderstanding about these that it will repay to give our impressions. We are confining our description of symptoms to the disease when it has involved only the uterus and cervix. Quite another train of symptoms arise out of regional extensions. These are purely incidental to this study. The disease, when in the chronic state, is usually symptom-free. The symptoms associated with chronic metritis usually arise out of associated diseases, such as prolapse owing to improper involution of the supporting structures, or backache due to an extension of the infection into the post-uterine parametritic tissues. But when the uterus and cervix alone have been involved, there are not usually any symptoms. The menstrual cycle and flow usually have not changed. The disease is usually found accidentally, when a gynaecological examination is undertaken because of some coincidental symptom or sign. Haemorrhage, which, in the minds of gynaecologists, is commonly associated with chronic subinvolution, has nothing to do with the chronic uterine disease. The association is purely accidental. The chronic subinvolution will frequently have been present for years unrecognized, until the haemorrhage necessitated an examination.

William Fletcher Shaw, in a lecture upon chronic metritis delivered at McGill University, said that operation for removal of the uterus in these cases is a confession of defeat. So it is. The menorrhagia and metrorrhagia have a cause external to the uterus, and the uterus, in preference to any other organ, bleeds because of its habit of bleeding. The causes may be numerous, but may be summed up under the term toxic. That implies chemical, microbic and metabolic toxicities, and under metabolic we must include all endocrine imbalances. What are the causes of these haemorrhages? In what way does the toxicity operate? Virchow once stated that in some cases the cause is in blood changes; in others, it is capillary dysfunction, and in still others, it is both blood and blood-vessel alteration. Osler[3] said of these vascular extravasations, "Some day an anaphylactic key will open the door to this dark chamber."

We now step from the realm of facts into that of fact and speculation, which is much more fascinating, owing to its larger mental scope.

2. *Symmetrical and Asymmetrical Enlargement of the Uterus Owing to Endocrine Imbalances.*

Into this class we place the following:

A. Symmetrical enlargements: (*a*) general; (*b*) endometrial endometriosis; (*c*) diffuse uterine parietal endometriosis.

B. Asymmetrical enlargements associated with (*d*) fibroids, myomata, fibromyomata; (*e*) endometriomata; (*f*) combinations of (*c*) and (*d*), such as adenomyomata, and adeno-fibromyomata.

This classification is very simple, and has for its great virtue a common activator—endocrine imbalances. We believe that common agent to be an excess of oestrin—a hyperoestrinism—for the reasons that will be given later. It is also pointed out that the range of abnormal quantities of oestrin in the blood can be a very wide one, without producing symptoms or pathological states, just as very wide ranges in blood-sugar may be found without eliciting symptoms. Behind each of these calculations lies the individual herself, and behind her again, her component cell tolerance of any abnormal internal environment, and by the internal environment we mean, as did Claude Bernard, the circulating blood with, in this case, its normal endocrine content.

There is another factor which will make computation extremely difficult. It is commonly known that it is not the abnormal blood content which elicits symptoms or pathology, but the intimate intracellular contact of this abnormal environment. And

it is also known that there is a direct antagonistic action between oestrin and progesterone. For example, if a large quantity of oestrin be injected, a surprisingly small quantity of it can be recovered in the urine. But when it is followed by an injection of progesterone, the liberation of oestrin or its derivatives in the urine is prompt and almost complete. This must be interpreted as a power of certain specific cells to retain the oestrin until forced to give it up by a subsequent command. If this be true, then it is logical to assume that hyperoestrinism may be entirely intracellular—retained in the specific cells of the pelvic organs—and that urine estimation of oestrin content would be very misleading in these circumstances. So we may conceive that there may be a real or a relative hyperoestrinism, due to an inefficiency of progesterone to release the intracellular oestrin.

In all these instances, of group B, it will be recognized that the diseases associated with the hypertrophied uterus are of frequent coincidence, so much so that we now believe that the coincidence is not accidental, but is a dual or common response to a single causative agency, and that this response may affect one or all of the uterine cellular elements. The enlargement of the uterus in these circumstances is not that of chronic subinvolution, which is an arrest of a retrograde process of restitution, but it is a hypertrophy of the normal constituent elements of the uterine wall under the stimulus of hormonal action, similar in many respects to that of pregnancy, but differing in minor selective details. That it does not cause hypertrophy similar to that of pregnancy is shown in this observation, that pregnancies, so far as we know, cause the uterine cellular constituents to hypertrophy in a definite ratio one to another. This is not true, however, of the abnormal hypertrophies enumerated above. In some of these, the hypertrophy may simulate a pregnancy. Such are the cases which fall into group A, the symmetrical enlargements. However, though this type is well known, it is not the rule. In most instances one or other of the constituent elements acquires a preponderance, and in addition to the general hypertrophy, there may be a local stimulation of the fibrous elements or of the muscular elements to form tumours, and thus to cause the uterus to become asymmetrical.

The interesting part of this study is the generalization that all these diseases have an abnormal endocrine agency, and that the variations in their manifestations are just evidences of tissue selectivity for the operation of these agencies. And,

owing to the similarity of this abnormal hypertrophy to that of normal pregnancy, we are led to the inference that the difference is probably quantitative, rather than qualitative.

This selectivity of the tissue for hormonal preference is seen in a great many ways. Let us first of all analyse the hormones themselves. We have two known ovarian hormones which play the principal roles in the uterine menstrual cycle, and in the uterine changes of pregnancy. These are the follicular hormone, oestrin, and the corpus luteum agent, progesterone. The former, oestrin, is the growth hormone, causing hypertrophy and multiplication of the uterine elements. But it is only when the hormone is in great excess of the needs of the non-pregnant that its action extends beyond the inner two-thirds of the endometrium. Let us clarify this matter, for it is essential to an understanding of the sequel. In a menstrual cycle, nature does not expend any more energy than is necessary to bring about a physiological result. The result to be achieved and the *raison d'être* of this cycle is to prepare the endometrium to a suitable state of semi-fluidity to permit nidation, and nutrition of the ovum. As nidation of the ovum in its initial stages involves only the surface of the endometrium, we find that the cycle prepares only the inner third, and to a lesser degree, the middle third, and does not affect the basal third of the endometrium. This is a conservation of energy. And when conception does not take place, the surface third, which has gone a long way in differentiation, cannot revert, so it is cast off. Reversion is probably impossible. During this follicular stage growth hypertrophy is the predominant feature. In the luteal stage hypersecretion is the dominant feature to produce a succulence for easy nidation and nutrition of the ovum. Having considered the functions of these hormones, we may add that they may be intensified or mitigated by the action of other hormones, such as, for example, the thyroid and pituitary.

Let us now bring this knowledge to bear upon this group of diseases. We noted above the selectivity of the ovarian menstrual hormones for the surface layers of the endometrium. There is quite another feature of this endometrial selectivity which is not commonly known. It is that one may find in one microscopic field of the endometrium a cyclic reaction which is intense, and reaches down to the myometrium, and close beside it may be an area that does not show any appreciable cyclic change. Such islands of unaffected tissue are frequently found in this endometrial change. This clinical tissue selectivity is just

as inexplicable as bacterial selectivity, but basically both are chemical affinities. But why should an island of tissue differ from its immediate environment?

There is another interesting feature of this selectivity, and that is that this susceptibility to hormonal influence can be carried over by an endometrial cell when that cell has been transplanted ectopically. Let us give a specific instance. Endometriosis spreads ectopically in a manner similar to bacterial infections. Goodall, in his monograph on puerperal infections,[4] pointed out that infections spread by one of four ways.

1. By local infections.
2. By the lymphatics.
3. By the veins.
4. By continuity of surface, that is, by the tubal spill.

In endometriosis we may have purely endometrial hypertrophy due to hyperoestrinism, corresponding to group 1, a local infection. Then again, the disease may spread from the basal endometrial layer into the myometrium and beyond the uterus, by the lymphatic channels, as in group 2. Then again, the endometriosis may spread by the veins, as has been demonstrated by Sampson[5] and Goodall, therefore corresponding to group 3 of bacterial infections. Lastly, endometriosis may spread by continuity of surface through the Fallopian tubes, constituting the spill method, as so frequently occurs in low-grade infections, notably gonorrhoea and infections of similar tenacity and virulence. The implants which soil the pelvic peritoneum practically all arrive by the spill method of spread. Practically all of these, when so implanted, respond to the cyclic menstrual changes, and give rise to bloody extravasations. Why? Because the cells have been derived from the desquamated surface layer of the endometrium and these are very susceptible to ovarian hormonal effects, and they carry over this trait to their new peritoneal soil. Whereas, uterine endometriosis involving the uterine musculature is derived from the deepest layer of the endometrium which does not normally respond to the ovarian hormones, and even in abnormal cases, only to a slight degree. So when the endometrium abnormally invades the deep uterine lymphatic spaces they never respond to the cyclic changes, and never bleed menstrually. If these invasions responded to the hormones, the uterine musculature in such cases would be infiltrated by blood cysts, because the ectopic endometrial nests have no outlet. But blood cysts in-

volving the crypts of the endometriosis in the uterine wall are an extreme rarity, and when found are always the result of an haemorrhagic tendency that is quite independent of the menstrual cycle. This we have proved beyond any possibility of doubt, by the coincident involvement of many tissues in addition to the uterus, in a diffuse corporeal haemorrhagic state, or by excessive bleeding at operation.

If we study group A, the symmetrical hypertrophies, some further explanation is required to understand their full import. The general type of this group is one of fairly common occurrence in which the uterus is generally and symmetrically enlarged, simulating in every detail of bimanual examination an early pregnancy, though in this case the enlargement is slow and has a limit to its progress. Menstruation is not affected and the only diagnostic sign between it and early pregnancy is the absence of the Aschheim-Zondek sign. The mucosa of the uterus is generally slightly thickened, but the uterine wall is universally hypertrophied. Ovarian examination may show some ovarian enlargement, due to persistent follicular phases. Often there is a hypothyroidism, the treatment of which frequently causes regression to normal uterine dimensions. The softening and enlargement of the uterus in the premenstrual state is a normal and miniature cyclic forecast of this more permanent enlargement. The one is normal, the other is the expression of an abnormal persistence of abnormal hypertrophy in response to hormonal dysfunction. In the second group (*b*), the growth stimulation spends itself chiefly upon the endometrium, causing it to hypertrophy to great thickness, often of the Swiss-cheese type. This is not an inflammatory change. It is an expression of a chronic hyperoestrinization, and group (*c*) is another expression of the causation. In group (*b*) the overgrowth is chiefly into the cavity of the uterus, whereas in group (*c*) the basal layer of the endometrium infiltrates the uterine wall along the lymph and venous channels. There may be all degrees of this penetration, from a quasi-normal to a diffuse and copious infiltration in all directions.

Why, we may ask, should these hypertrophies extend in the one instance into the uterine cavity, and in the other case infiltrate the uterine wall? There can be no adequate answer to such a question, except to ask why does cancer in one case grow outwardly, and in another case spend all its energy in infiltration? The answer is equally obscure. In these cases of group A all the constituent cells of the uterine wall respond to

the stimulus and show signs of cell hypertrophy, and consequent symmetrical enlargement of the uterus simulating the hypertrophy of early pregnancy.

In group B, the asymmetrical growths, we find the common association of uterine hypertrophy with fibroids, myomata and the admixture of these with endometriomatous elements, or we find uterine hypertrophy in association with endometriomata. We would here point out for purposes of clarification, that endometriosis implies a diffuse infiltration by endometrial tissues, whereas endometriomata are local collections into tumours of these same elements. Only the latter types produce asymmetry and simulate, on bimanual examination, the more common elements fibromata and myomata.

The combination of the endometroid elements with fibroids and myomata have been denominated in the past as adeno-fibro-endometrio-fibro-myomata. This designates their common agency in cause, and accidental inter-infiltration, in growth.

In one case, the activating agent may stimulate fibrous tissue locally, to give it preponderance over the general uterine hypertrophy, and in another the muscle tissue may become similarly and locally affected, thereby producing fibroids and myomata, respectively. In a similar manner the stimulus may affect both the glandular and the stromatous cells of the endometrium simultaneously, thereby producing the mixed types of endometriosis, whereas, in other cases, only the stromatous elements may be over-stimulated to produce tumours made up solely of stroma cells and, therefore, called stromatous endometriosis or endometriomata. In the endometriomata there will be uterine asymmetry.[6]

The common association of uterine hypertrophy with fibroids, myomata and endometriosis points strongly to a common stimulating agency. But more interesting than this association is the lack of incidence of pregnancy with these diseases—a fact which bespeaks an abnormal endocrine imbalance. Theoretically, one may assume that, for conception to occur, there must be a delicate balance between the two ovarian secretions. If there is preponderance of the follicular over the luteal secretion, we would naturally suspect overgrowth with or without disturbance of menstruation. Whether this alone would be sufficient to prevent conception is questionable. But in cases of fibroids or endometriosis the Fallopian tubes are usually patent and, therefore, there is no physical obstruction to the meeting of the oocyte and the sperm. Yet pregnancy in cases of fibroids, and

pregnancy in association with endometriosis, is relatively rare, more so in cases of endometriosis than in cases of fibroids. In Goodall's series of cases of stromatous endometriosis there had been an average of 14 years of sterility in the 14 cases reported, and we have seen and heard of only 3 cases of pregnancy complicated by endometriosis. The inference is that the soil favourable for fibroids and endometriosis is not that which is conducive to pregnancy. Since the physical conditions in these diseases are favourable for the meeting of the constituent elements of pregnancy, then the causes must be biochemical, and that, in the last analysis, is bound up in the hormones. Whether this is purely variation in the quantity or quality of the ovarian secretions, or whether the rhythm and synchronism of these is lost, or whether the disturbing influence comes from restraint or over-stimulation of the other non-pelvic glands, are matters which must await further elucidation.

A fact which lends some weight to this last conjecture is found in the following research. In a lecture before the Canadian Medical Association last May[7] (awaiting publication), Goodall pointed out that in a series of 10 cases of endometriosis in which the basal rate was taken, it was found quite low in each case. Acting upon this knowledge, 2 of these patients who had been operated upon conservatively, so as to retain the ovary least affected, were put upon large doses of thyroid, and both are now pregnant, one 2 years, and the other 2¾ years after operation. Is it possible that the cause of the pelvic pathology is primarily thyroid and secondarily ovarian?

Goodall has frequently emphasized the fact that our concept of endometriosis is too restricted. He has pointed out that endometriosis is an expression of hyperoestrinism from the following facts: that oestrin is the growth-stimulating hormone; that it is the chief agent in producing the uterine hypertrophy of pregnancy in its early stages—a function probably taken over later by the placenta; that the uterine mucosa undergoes hypertrophy during the follicular stage of ovulation, at which stage the oestrin is on the increase; and that the uterus enlarges as a whole and becomes softened during this stage.

It is our firm conviction that a virgin uterus that has become infected by gonorrhoea or other similar acute ascending infection, cannot appreciably increase its bulk, no matter how acute or how prolonged the infection. When, however, the infection has reached the appendages, its propinquity to the specific structures of ovarian function may stimulate these, or vitiate them,

to the degree that the relative quantity or rhythm is lost, and hypertrophy of the uterus may readily follow. Heretofore, this uterine change has been attributed without question to the infection. Though the infection is the activating agent, it is not by its direct action upon the uterus, but through the intermediary of the ovary, that the uterine enlargement has taken place. Removal of the ovaries, in these circumstances, invariably brings about involution of the uterus, no matter what the character of the residual infection in the uterus.

Let us revert to the cases of endometriosis. Endometriosis, wherever seen clinically in the pelvis, is merely the most pronounced expression of the disease. If we examine the pelvic tissues taken from a case of active endometriosis, we find that there are generalized changes throughout the pelvic tissues. Not only are the organs affected, but the connective tissues will show changes, less pronounced, it is true, but proportionate to those of the specific organs of generation. Naturally these changes will vary with the intensity and duration of the hormonal imbalance.

What are these coincidental changes? Let us suppose that the most pronounced clinical pathology is found about the ovaries and Fallopian tubes. The inference is that this is a spill. There will be dense adhesions which are characteristic, and there will be tissue and outline destruction by blood cysts. But a careful microscopic examination will also reveal all, or several, of the following changes, elicited in response to the same hormonal imbalance that caused the peritoneum to become susceptible to implantation. These are in the order of their frequency. Cystic endometrial hypertrophy of a chronic nature, adenoma of the cervix, endocervicosis (a new disease described by Goodall in an article to be published in the *Journal of Obstetrics and Gynaecology of the British Empire*), uterine myometrial endometriosis, transplants of endometriosis in the cervix, vagina and other tissues in the immediate neighbourhood, connective tissue changes, and lastly, peritoneal sclerosis. This last is interesting. It is most intense in the pouch of Douglas and vesico-uterine, the most dependent parts of the peritoneal sac, into which the ovarian hormones gravitate and exercise a powerful influence. This sclerosis diminishes as one rises to the height of the umbilicus, above which it can no longer be recognized. Not infrequently we have been able to diagnose pelvic endometriosis by the thickness of the anterior parietal peritoneum at operation. The same occurs, though to a less

degree, in fibroids of the uterus. In many cases of fibroids we have seen this peritoneal sclerosis, which may appear as white as parchment, spreading out like two fans over the posterior uterine wall, with the fan-handles at the utero-ovarian ligaments. If the uterus is retroflexed in the pouch of Douglas, the whole uterine wall will usually show this peritoneal sclerosis.

Here, however, we must interpose a word of caution which arises out of a careful study of a large number of cases of endometriosis. Only a percentage of cases of endometriosis are active at the time of operation. If one sends to the pathologist the tissues of undoubted clinical endometriosis removed at operation, one is disappointed in that in only about one-third of these is the diagnosis confirmed. Yet we consider that there are certain attributes of peritoneal endometriosis which are characteristic. These are chocolate cysts, old encapsulated peritoneal blood accumulations, and the sites and characters of the adhesions, and peritoneal sclerosis. The chief sites of endometrial adhesions are on the ledges of the utero-sacral ligaments, and the characters of the adhesions are diagnostic. There is nothing that resembles them except malignancy and tuberculosis. In these three diseases all lines of normal cleavage are lost, and two juxtaposed surfaces literally fuse. The lumina of the Fallopian tubes are usually free in endometriosis, but in tuberculosis they are almost invariably closed. Malignancy does not enter into the question. What, then, is the explanation? The explanation has a far-reaching bearing upon treatment, and must be given with precision. It is that the hormonal imbalance that primarily gave rise to the endometriosis is often merely a temporary aberration, and nature, in two-thirds of the cases of endometriosis, restores the hormonal balance spontaneously, and in these circumstances the disease is not only arrested, but regresses. The ovarian blood-cysts, if not too large, become absorbed, their contents become tarry by absorption of the fluid plasma, causing inspissation; the endometrial ectopic elements first cease to function in response to the menstrual hormone, and then are slowly destroyed, but the fibrous tissue which develops in all new growths, sometimes more, sometimes less, always remains to perpetuate the fusion of the infiltrated structures. Hence, clinical endometriosis is three times more common than the microscopic diagnosis would indicate. And the deduction is that where we recognize the signs of the arrest of the disease, we can afford to be conservative in operative removal of organs.

Since we believe that fibroids are a local excessive response to the growth ovarian hormones, and since arrest of the endocrine imbalance is followed by regression of the disease in endometriosis, and since it has been pointed out that fibroids and endometriosis have so much in common and are always accompanied, in their active stage, by uterine hypertrophy, we believe that the degenerations of fibroids are not always due to defects in vascularization, but are chiefly due to spontaneous restoration of normal hormonal balance and withdrawal of the abnormal stimulating agent which brought them into being. We think we have a criterion for this situation. If the uterus is still greatly hypertrophied in the presence of fibroids, the chances are that the disease is still active. If, on the other hand, this hypertrophy of the uterus has passed, and involution has taken place, then we can assume that the hormonal balance has been restored.

This hypothesis brings a very disquieting afterthought; it is that myomectomy, multiple myomectomy, is merely removing the effects, but not touching the underlying cause. It also brings up the further disquieting thought, that pregnancy may occur in fibroids, not on account of the fibroids, but on account of the underlying endocrine imbalance. Since endometriosis and fibroids have so much in common, and since pregnancy and endometriosis are so infrequently associated, may this not explain the infrequency in the incidence of pregnancy and fibroids? And when pregnancy does occur in these circumstances, does it not imply a normalcy regained, and does it not explain the frequent disappearance of these tumours in the puerperium? Emge[8] has proven that fibroids do not grow during pregnancy, which is another argument in support of the withdrawal of the abnormal stimulation which brought the fibroids into being, and the withdrawal of which restored conditions favourable to conception.

There are other factors which bear directly upon our subject. Involution of the puerperal uterus is intimately bound up with ovarian function. During pregnancy the ovaries enlarge very considerably. This is quite independent of the corpus luteum. Many Graafian follicles awaken to activity and go on to partial maturation, only to develop luteinization of their theca interna, and then regress. After labour the ovaries regress with the uterine involution. These stand in relation to each other as cause and effect. When, after pregnancy, the ovaries hyperinvolute from causes as yet unknown, the uterus and all the pelvic

organs may reach a stage of climacteric degeneration which may be temporary or permanent. The question which at once arises is whether, in some cases, subinvolution may not be the reverse of this hyperinvolution, and if hyperinvolution is an excessive ovarian regression, may we not also have insufficient ovarian puerperal regression which would keep the uterus in a constant state of enlargement, akin to that stimulation which brings the hypertrophy of fibroids and endometriosis into the field? That is the problem which is now occupying our attention. It is one that is filled with unexpected possibilities.

Conclusions and Theories

1. Chronic subinvolution, as the term implies, is an incomplete involution of the puerperal or post-abortal uterus. It is known under various names, such as chronic metritis, fibrosis uteri, and arterio-sclerotic uterus.

2. The commonest cause is a chronic low-grade infection, causing a lymphatic block, parallel, in many ways, to venous thrombosis.

3. Chronic subinvolution is the expression of a faulty and incomplete breaking down after pregnancy at term, or an abortion. Whereas the symmetrical uterine enlargement (group A) and the asymmetrical enlargement of the uterus which accompanies fibroids and endometriosis (group B) are responses to a stimulus, and most probably to the growth-hormone oestrin, which also is responsible for the fibroids and the endometriotic ectopias. In other words, the uterine enlargements, the endometriosis, the fibroids and the myomata, are different expressions of a common cause.

4. This stimulus makes itself felt in changes in all the pelvic organs. These generalized changes may be imperceptible in the milder cases, except as a local manifestation, but are easily recognizable in the more severe and prolonged endocrine dyscrasias. They may involve the pelvic peritoneum as a diffuse cartilaginous sclerosis. They stimulate the quiescent parovarium into secretory and cellular activity, the Fallopian tubes into invasive growth, the endometrium into a thickened endometrium characteristic of persistent follicular over-activity, or the endometrium may grow ectopically either in the uterine wall or in any of the pelvic tissues below the umbilicus. The cervix may become the seat of polypi, adenomata and of endocervicosis (Goodall);[9] and lastly, the vagina shows epithelial changes characteristic of hyperoestrinism.

5. It is commonly stated that the fibrous tissue growth that accompanies new growth is the result of the irritation of the new growth, and is the expression of a confining reaction to it. But this is not so, as regards the uterine enlargement. This is the direct action of the ovarian hormones.

6. If this is true, then removal of fibroids by enucleation is merely removing the most obvious local manifestation of the disease, and by leaving the hypertrophied uterus, unless the cause had ceased to operate before operation, it will continue to reproduce its abnormal manifestations after surgical intervention.

7. Sixty per cent of cases of clinical endometriosis are quiescent at operation. Nature has spontaneously restored the endocrine balance. This spontaneous recovery is characteristic of endocrine imbalances. The congenital gland instability underlying the temporary dyscrasia usually persists and imbalances may reappear under favourable environmental changes.

8. Endometriosis, fibroids and fibromyomata are commonly accompanied by sterility. It has been taught that these diseases are the causes of sterility, but we think that the sterility is due to the endocrine imbalance that produces the new growth, and that the advent of pregnancy is an expression of restoration of normal or quasi-normal balance, and is the most potent external expression of regression in the new growths. We think that the arrest of growth of endometriosis and of fibroids during pregnancy, and the subsequent disappearance after labour, are further expressions of that endocrine restoration.

9. The withdrawal of the abnormal endocrine stimulation at the climacteric, or through artificial surgical menopause, leads to the same regressive results as are obtained after spontaneous restoration of endocrine balance.

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Dysgerminoma: a Complete Report on a Case of Bilateral Dysgerminomata complicating Pregnancy with Malignant Secondary Deposits and Fatal Termination*

BY

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OVARIAN tumours not infrequently obstruct delivery. The treatment of such a complication of labour does not, as a rule, give rise to any great difficulty. If the tumour can be displaced above the pelvic brim and the presenting part then enters the pelvis, labour may proceed and terminate normally. The tumour can later be removed by laparotomy. If the neoplasm cannot be displaced, and if it is cystic in character, it may be aspirated through the vaginal fornix and delivery take place past the emptied cyst.

If the tumour be of the solid type and cannot, for any reason, be displaced from the pelvis, Caesarean section is the treatment of choice.

Such a complication was found in a patient admitted to the National Maternity Hospital on January 14th, 1939. She was a primigravida, aged 27 years. She had been married for 2 years, had always had good health and her menstruation had been regular and normal. Apart from one slight haemorrhage about the 10th week, her pregnancy had been uneventful until the 36th week.

When 36 weeks pregnant she had repeated attacks of vomiting, which progressed until her admission at the 39th week. It was on account of this symptom that she was admitted to hospital.

* A preliminary report of the clinical aspects of this case was made to the Gynaecological Section of the Royal Irish Academy of Medicine, and published in the " Irish Journal of Medical Science," December, 1939, p. 848.[1]

FIG. 1
Showing the naked-eye appearance of the cut surfaces of the tumours from both left and right ovaries.

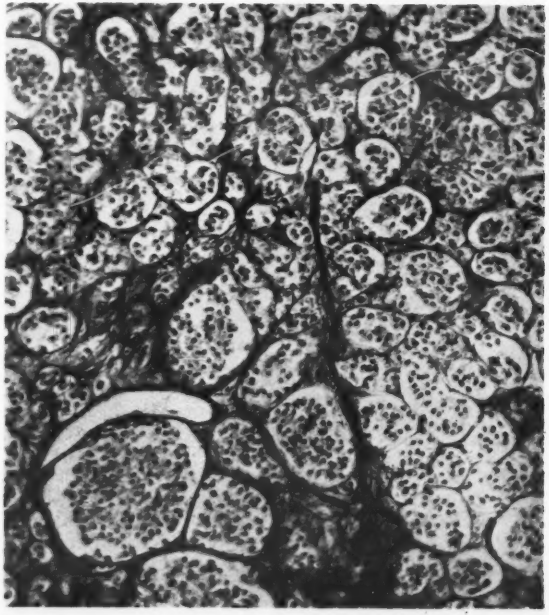

FIG. 2
Microphotograph illustrating the histological structure of part of the original tumour.

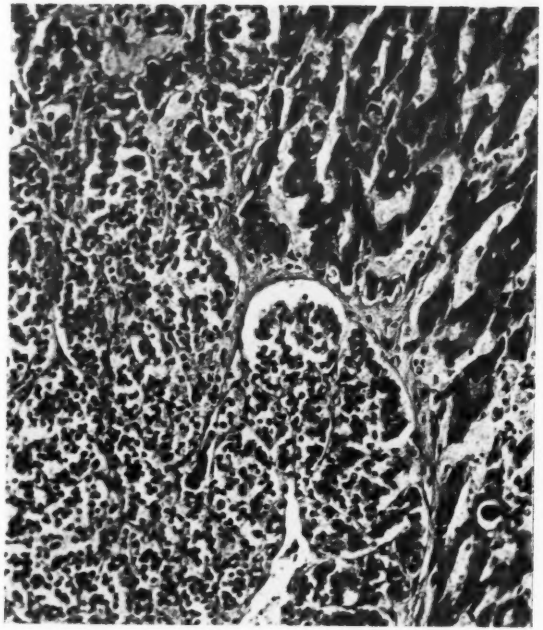

FIG. 3
Microphotograph illustrating the histological structure of the liver deposits.

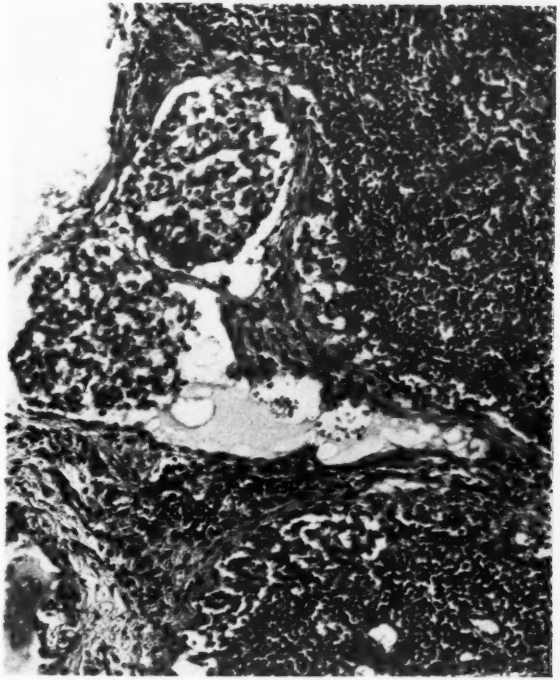

FIG. 4
Microphotograph showing a small deposit in a lymph gland. (Para-aortic.)

c.

On admission, her general condition was poor. She was somewhat wasted and appeared cachetic. Her blood-pressure was low, the urine was normal. The abdomen was tense, rigid and difficult to palpate. The foetus was in the 2nd vertex position with the head floating above the brim of the pelvis. A large hard mass could be palpated in the right flank; it felt like the back of a second foetus. Since the vomiting was troublesome the patient was treated for this condition and nothing further was done.

The patient started labour spontaneously 2 days later. The head of the child remained unfixed. Rectal examination revealed a large solid mass in the pouch of Douglas. This tumour could not be displaced. A lower segment Caesarean section was immediately performed and a healthy living male infant extracted, weighing 8 pounds 4 ounces.

Two large ovarian tumours were then exposed. The right tumour extended from Douglas's pouch to the level of the right kidney. It was solid but soft and had a brain-like appearance. It was covered by a thin transparent membranous capsule. It was adherent to the back of the cervix and to the pelvic peritoneum. The tumour on the left side was about the size of a grapefruit. It had the same general characteristics but was lying quite free in the abdominal cavity. Both tumours had fairly long pedicles. The removal of the left tumour did not present any difficulty. The right tumour, on account of its size and pelvic adhesions, caused some difficulty. It was removed completely with its capsule intact. Its removal resulted in considerable venous oozing which was difficult to control. On account of the patient's generally low condition it was decided not to perform a hysterectomy, although the tumours at the time were believed to be most likely malignant. The tumours were examined by one of us (J. McG.), who reported as follows:

"This specimen consists of two tumour masses. The larger is roughly kidney-shaped, measuring about 27 cm. in length × 14 × 12 cm. The smaller is roughly ovoid, measuring about 14 × 12 × 9 cm. Both tumours are identical in their general and histological characteristics. The surface is covered by a thin pseudo-capsule carrying fairly numerous blood vessels, and it is roughly lobulated. When cut into, the tumours are seen to be composed of firm, rather elastic whitish tissue. The central areas of both tumours show mucoid degeneration, and this degeneration has produced irregular cystic cavities.

"Several sections were prepared from both tumours. These

sections show a sponge-like stroma of fibrous tissue. Supported in the cavities of this fibrous tissue framework are masses and islands of cells. These are relatively large in size. For the most part they show clear protoplasm and, as frequently happens with these tumours, the cells have shrunken in the process of fixation. In most areas the nuclei are also shrunken and they stain densely. In a few areas, however, the nuclei are better developed and are then seen to be relatively large with well-marked nucleoli and nuclear membrane.

"These histological features are exactly similar to those of certain seminomata and, taken together with the general characteristics of the tumours, clearly indicate that both tumours are dysgerminomata."

The patient made a rapid and uneventful recovery following her operation. Her general health improved and she was given a course of deep radiation, as such tumours are supposed to be sensitive to radiation.

The patient's improvement, however, was only temporary. Within about 4 months she showed signs of general abdominal involvement with ascites. She rapidly became weak, anaemic and cachetic. She died on the 5th of March, 1940, 14 months following her operation.

At the post-mortem examination the patient was found to be very emaciated, with oedema of the legs and massive ascites. The abdomen was protuberant like a full-time pregnancy. The skin was yellow. There was marked mammary atrophy. The peritoneal cavity contained rather more than 2 gallons of a straw-coloured cloudy fluid. Veils of light adhesions intertwined the coils of intestine. The liver showed gross lobulations and it was considerably enlarged. The glands along the aorta were also enlarged, adherent to one another and to the pancreas.

The liver was found to contain massive multiple secondary growths which composed about 9/10ths of its volume. Some of the secondary growths had extended to the transverse colon and the diaphragm adjacent. The spleen was enlarged and there was some peri-splenitis but no evidence of secondary deposits. There was a small secondary deposit about 1 cm. in diameter in the lower lobe of the right lung. The heart and kidneys were free from secondary deposits. The uterus was small and atrophic and buried in dense adhesions.

Histological examination showed that the secondary deposits in the liver, aortic glands and that spreading from the glands

into the pancreas were cytologically identical with the primary growth in the ovaries.

Many of the masses in the liver presented a unique naked-eye appearance on cross-section. They were rounded with a rind of fibrous tissue (pseudo-capsule). Below this rind the tissue is degenerated and is supported by radial lines of fibrous tissue leading from a core of fairly firm whitish tissue. The central zone of degeneration is hyaline in character, and thus the tumour mass presented somewhat the appearance of the cut surface of a slice of lemon.

The case is of special interest because of:

(i) The rather large size of the tumours. (They rarely exceed the size of a Jaffa orange.)

(ii) Their bilateral occurrence.

(iii) Their occurrence during or in association with pregnancy.

(iv) The remarkably large secondary deposits which developed in the liver within a year.

Ovarian dysgerminomata are not very common tumours. Until recently, less than 80 cases were to be found in the literature. Recent reports, however, show that the tumour is not quite so rare as was believed.

Dockerty[2] estimates that the literature contains records of about 200 cases of dysgerminoma. Of these he estimates that 45 per cent are malignant, more especially those which were found to be bilateral (about 35 per cent of the total number). The great majority of the cases recorded were associated with hypoplasia of the genital organs.

According to investigations recently carried out by Novak and Gray,[3] Foderl,[4] and by Greenblatt and Purd,[5] the dysgerminomata arise from cells misplaced at the time of sexual embryonal growth of the gonad when the mesenchyme is as yet undifferentiated and neutral. A similar tumour, the seminoma, occurs in the testis. Dysgerminomata, therefore, behave in marked contrast to the granulosa cell tumour, which due to its hormone has a feminizing influence, and to arrhenoblastoma which has a masculinizing influence. The dysgerminoma, since it does not produce any hormone, has no influence on menstruation or otherwise. This absence of ovarian hormone was investigated and proved in a case recently reported by Spielman and Morton.[6]

The tumour appears early in life. Most of the tumours reported were in patients between the ages of 10 and 25. These

tumours are slightly more frequently unilateral. While the unilateral type are sometimes benign, the bilateral are almost always malignant.

Summary

1. A complete report is given of a case of bilateral dysgerminomata obstructing delivery. The tumours had been removed at the time of delivery by Caesarean section on the 16th of January, 1939.

2. The patient died on the 5th of March, 1940, and a post-mortem examination revealed marked cachecia, ascites and massive secondary deposits in the liver and in the aortic glands.

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A Case of Arrhenoblastoma

BY

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CASES of arrhenoblastoma are sufficiently rare to justify publication. Moreover, I have not been able to find any published report of a case in Australia.

Reported Cases

A brief summary of reported cases is given as no résumé has been reported in recent English journals.

The first reported case was described by Pick in Germany. In a solid ovarian tumour he found a tubular arrangement of epithelial elements and noted a microscopic resemblance to seminiferous tubules in the testis. In 1907, Shickele reported similar microscopical findings in another solid ovarian tumour. Bell, in 1915, in England, described a third case and he noted that the patient had shown masculinizing changes. In addition to the tubular arrangement in microscopic sections, he described interstitial elements which contained lipoid substances. In the same year, Robert Meyer[1] collected 17 additional cases, many of which were associated with virilism. He also suggested that the number of interstitial elements present in the tumour had a direct relation to the associated virilism in the patient. The first case in America was reported by Moots in 1921, and since then Robert Meyer, Goodall,[2] Baldwin and Gafford,[3] Norris,[4] Camelo and Lisser,[5] Maxwell,[6] Dockerty and McCarty,[7] and others have reported cases in the American journals, and several of them have given complete reviews of the cases reported to date.

Origin

Robert Meyer, Goodall, Novak and others believe that these tumours arise from embryonic remnants of the seminiferous tubules in the hilus of the ovary. McLester suggests that it represents a one-sided development of a teratoma. The general opinion is that these tumours are probably derived from a primitive ovo testis, the male element being inactive until the

tumour begins to grow and form a testicular tumour, the hormone of which has masculinizing properties. Wilfred Shaw[8] states that most pathologists dislike the theory of embryonic relics as so few claim to have found them in the adult ovary. He believes that the view that embryonic relics have been present and quiescent from foetal times may be wrong and suggests that dividing cells may revert back to early cells of the foetal type. In granulosa cell tumours, which develop after the menopause, such a process must be at work, for "the new cells produced by division are anterior in type to the cells of the senile ovary." He suggests that "the same process may occur in the adult ovary, whereby adult cells revert back by division to cells which are embryonic in type." Definite conclusions have not been reached and the matter is still unsettled.

Diagnosis

There is some difference of opinion as to whether all cases reported are those of an arrhenoblastoma, as some did not reveal the masculinizing syndrome and most authorities are in agreement that it is impossible to make a diagnosis on the microscopical appearances alone.

In 1931, Robert Meyer in his classical article on "Some Species of Ovarian Tumours and their Relations to Sex Characteristics", stated his belief in the inter-relations of the various types, and divided his microscopic findings into 3 groups.

Group 1. Adenoma tubulae testiculare. This is the most mature and differentiated form and shows a regular tubular arrangement. Clinically, the majority of patients with tumours of this group do not show masculinization.

Group 2. A middle group composed of typical and atypical portions and also solid forms. This is intermediate between Groups 1 and 3, both histologically and clinically.

Group 3. A typical group composed mostly of solid forms with some atypical portions. This group does not show any true tubules, though a few areas may reveal isolated tubules or just irregular epithelial cords. These are the tumours associated with the most pronounced masculine changes.

Schiller in 1935[9] concluded that "the masculinizing effects of the arrhenoblastoma are connected with certain potentialities in the organs, and not all women possess these potentialities. They are remnants of a primary bisexual anlage which disappear in some individuals and persist in others." Evidence that there are women without such an anlage and that masculinization by

an arrhenoblastoma is dependent on the presence of such an anlage is given by the fact that there exist typical cases of arrhenoblastoma the hosts of which do not show any evidence of masculinization.

Novak, in 1938,[10] stated that "in a small minority of cases even though the tumour is clearly arrhenoblastoma, histologically, abnormal sex changes may be almost absent."

Norris, in 1938,[4] in a complete review of all reported cases of an arrhenoblastoma to date, criticized the diagnosis of a number of them on the grounds that the clinical syndrome was not present. He considers that in the present state of our knowledge of these rare tumours, the term arrhenoblastoma should refer to a clinico-pathologic condition and that the clinical signs and symptoms must be present as well as the pathological findings. He considers that as the microscopical picture may vary so greatly, there is no justification for classifying them as Meyer did, and one cannot make a definite diagnosis from the microscopic findings alone.

On applying this combined test to the recorded cases, Norris reduces to 29 the number then reported.

Goodall's case conforms microscopically to Meyer's third group, and yet had no defeminizing or masculinizing symptoms or signs; while Phelan's case showed a definitely tubular arrangement and conformed to Meyer's Group 1, but had a typical defeminizing and masculinizing syndrome. Norris would not agree that Goodall's case was an arrhenoblastoma; indeed, its derivation implies that if a case has not revealed masculine changes the tumour should not be called an arrhenoblastoma. The case I am about to describe conformed both clinically and microscopically to Meyer's third group.

These brief references to the views held by some pathologists show that the classification, as well as the origin of these tumours, is still unsettled.

Signs and Symptoms

The profound biologic changes caused by the tumour have striking and characteristic effects on the patient and the results of its removal are dramatic. The tumour produces defeminization and masculinization in the host. Amenorrhoea, loss of fat in the breasts and thighs, and atrophy of the mammary glands, are among the former signs, while masculine changes are shown in the growth of hair over the face (distributed as in the male beard), abdomen, forearms and thighs, a deepening of the voice

and hypertrophy of the clitoris. The uterus and the uninvolved ovary become hypoplastic.

The tumour usually occurs in young women who have matured normally and who then develop amenorrhoea. Hair begins to grow on the face and abdomen, with definite male distribution, and they usually consult a doctor about these signs and perhaps because they have noticed a swelling of the abdomen.

Malignancy

Most authorities agree that these tumours are usually benign. Wilfred Shaw[8] states that they are almost always innocent in type and for this reason removal of the affected ovary with the tumour is all that is considered necessary. On the other hand, Norris[4] refers to the 'arrhenoblastoma' as "a small but highly interesting group of malignant tumours, in which, through the actions of the hormone produced by the tumour, defeminizing or masculinizing effects become manifest in the host." He considered that all arrhenoblastoma are malignant. Dockerty and McCarty in a report on 4 cases of arrhenoblastoma in the Mayo Clinic records[7] state "these tumours are of a low grade of malignancy and in most cases respond well to local surgical removal."

Differential Diagnosis

A masculinizing syndrome may be caused by:

1. Cushing's Disease—Basophilic adenoma of the anterior pituitary.
2. Adrenal cortex tumour.
3. Arrhenoblastoma of the ovary.
4. Thymic tumour.

1. *Cushing's Disease.* A polyglandular disease of pituitary origin with hyperplasia of the cortices of the suprarenal glands and over-activity of the thyroid. This condition causes amenorrhoea; increase in weight due to fat on the trunk, neck and head, but not on the limbs; hypertrichosis of the face and loss of hair on the scalp. There is a characteristic kyphosis and often a raised blood-pressure which may cause headaches. Glycosuria develops in some cases and occasionally the clitoris hypertrophies. Signs and symptoms common to Cushing's and arrhenoblastoma are amenorrhoea, hirsutism and (occasionally in the former) an enlarged clitoris. Blood-pressure is not

raised, and glycosuria is not a characteristic sign. An X-ray of the sella turcica and a diabetic glucose tolerance test, with increase rather than loss of fat, should make the diagnosis clear.

2. *Adrenal cortex tumour.* These are more difficult to differentiate since they cause a masculinizing syndrome, and in the absence of a pelvic tumour or a palpable renal tumour, examination of the blood for the hormones might be the only way of arriving at a decision. If the adrenal tumour were large enough, a urogram might be useful, or a perirenal air injection for outline of the adrenals.

In our case, a salpingogram confirmed the diagnosis that the swelling was an ovarian or broad ligament tumour.

4. *Thymic tumour.* A rare condition which may give rise to a polyglandular syndrome caused by change in the activity of the suprarenal cortex, pancreas and thyroid gland.

Treatment

This is necessarily surgical and consists in the removal of the affected ovary only, in the majority of cases.

The results are usually dramatic. The menses reappear, the breasts enlarge and the figure develops normal feminine curves again. The voice remains more or less baritone and as a rule the clitoris does not return to its normal size. While there is a decrease in the growth and distribution of hair, some degree of hirsutism usually remains. The uninvolved ovary and the endometrium again function normally as is proved by the return of regular monthly periods, and by pregnancy, which in some cases has followed the removal of the tumour.

The following history is of interest, because the syndrome was typical of that associated with a masculinizing tumour. The diagnosis was suggested by the junior resident in the ward, Dr. D. Alexander, when he reported that the case had been admitted under my care, and subsequent investigations proved that his diagnosis was correct.

Case History

Miss L.D., aged 26 years. She consulted a doctor about a swelling in the abdomen, which she first noticed about a year ago. The swelling gradually increased in size, but did not cause any discomfort. She was admitted to the Launceston General Hospital under my care with a diagnosis of a probable ovarian tumour, or, alternatively, a pedunculated fibroid of the uterus.

Previous history. The patient has always been a healthy girl and has not had any serious illnesses. She lives in the country and has led a healthy out-door life. Her periods began at 14 years and were regular until 2 years ago. Four years ago she became pregnant and had an illegal operation at 2 months. Two years later she noticed that her periods were progressively becoming scantier and 18 months ago they ceased altogether. She has not menstruated since then, nor had any vaginal discharge. Since she was 18 years of age she has had a slight growth of hair on the upper lip and under her chin. She states that her mother and her two sisters have more hair on their faces than is usual, but not enough to disfigure them. About a year ago, she noticed that the hair on her face was growing coarser and spreading over her cheeks. She began to shave herself, and now has a strong beard and has to shave every day. (Fig. 1.) She also noticed that the pubic hair was spreading. This now covers the whole abdomen. Quite lately she noticed that her forearms and thighs had become hairy. She has not noticed any change in her breasts. Her health has been satisfactory and her only reminder of her periods is a regular, rather severe headache, which occurs at monthly intervals.

She admits that she had regular coitus for years up to about 6 months ago. She always had normal libido and her only reason for ceasing such relations was that pressure on the tumour hurt her. She almost always has an orgasm and the loss of her periods made no difference whatever to this. Her feelings towards men apparently have not been affected in any way by the masculinizing tumour.

Heart and lungs—clear.

Urine—no albumin or sugar.

Blood-pressure—130/88.

Abdomen—there is a large firm tumour about the size of a small football lying to the right side. It is somewhat kidney-shaped and the surface is irregular but smooth. It is freely mobile and does not extend into the pelvis. It seems a solid rather than a cystic tumour. Its shape suggests an enlarged prolapsed right kidney.

Vaginal examination. The labia majora are flat and hardly to be identified as such. The clitoris (Fig. 2) is greatly hypertrophied, having a well-marked glans, and has the size and appearance of a 12-months infant's circumcised penis, about 1½ inches long. The frenum of the clitoris hangs like a curtain and is grossly enlarged. Bimanually, the vagina and cervix are normal

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 5

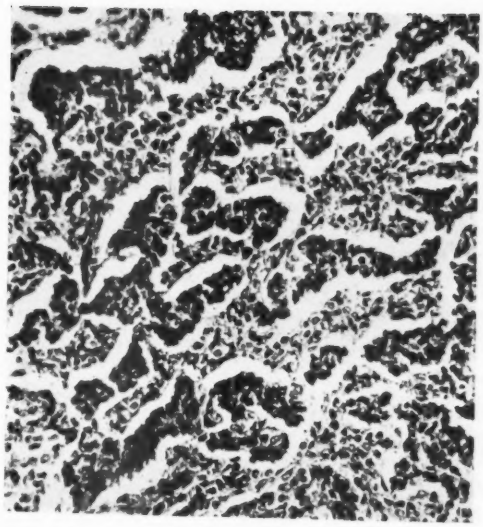

FIG. 1A

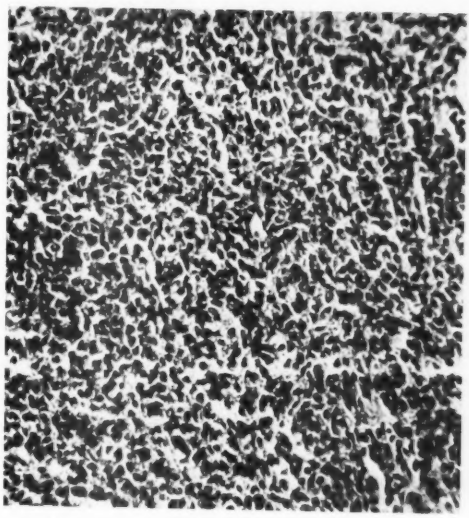

FIG. 2A

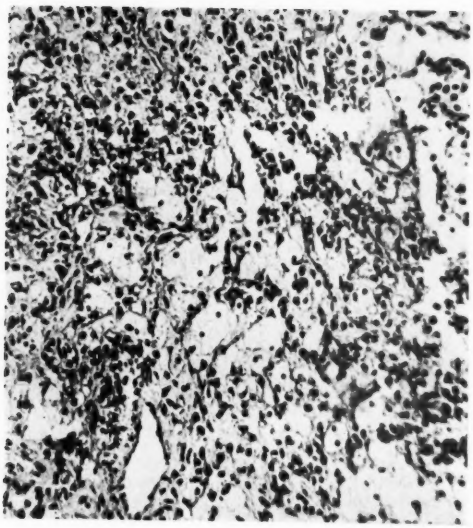

FIG. 3A

and the uterus seems a little enlarged, and lying to the left side, slightly retroverted. The tumour is not in the pelvis. From its shape it might be a solid ovarian tumour with a long pedicle, a pedunculated fibroid of the uterus, or less likely, a prolapsed grossly enlarged right kidney.

A salpingogram (Fig. 3) assisted in the diagnosis. This showed the lengthened right Fallopian tube passing upwards so that the fimbria was at the level of the 4th lumbar vertebra and near the midline. It was apparently closed at the fimbriated end. The left tube was normal in shape and position and was patent. The uterus seemed to be a little enlarged and lying to the left as found by the vaginal examination. A definite diagnosis was now made of a solid right ovarian or broad ligament tumour, probably in view of the age of the patient, its being unilateral, and the associated syndrome, an arrhenoblastoma. Unfortunately, we were unable to have any hormonal tests carried out.

Operative findings. Curette. Length of uterus, 9 cm. Very little endometrium and very free bleeding from the curetted surface. Laboratory report on the scrapings was as follows: "tubular glands present in normal stroma, a good deal of haemorrhage present."

Abdominal section. The findings conformed to what was expected from the salpingogram. The left ovary (3.75 cm. × 2.5 cm. × 1.25 cm.) was hypoplastic and looked like a senile post-menopausal ovary. The left Fallopian tube was normal. The right ovary was replaced by a large solid tumour (20 cm. × 15 cm. × 10 cm.). (Fig. 4.) Omentum was adherent to a small area of the posterior surface. The tumour was greyish in colour, with a smooth but somewhat bossy surface, and had a thick varicose pedicle. The right tube was lengthened and spread over the tumour. The cut surface was bright yellow and lobulated in some areas, some of these lobules having a stellate arrangement. It had the consistence of freshly cut spleen. Some areas were a paler yellow and softer, almost suggesting degeneration. Only one or two cysts were to be seen. Throughout the tumour, there was a remarkable absence of blood vessels, but a few were visible here and there between the lobules. (Fig. 5.)

The tumour was submitted to Dr. Rupert A. Willis, pathologist to the Baker Institute, Prince Alfred's Hospital, Melbourne, who reported as follows:

"The material submitted for examination consisted of four blocks of tissue preserved in formalin solution. These were

embedded in paraffin, sections were cut and stained by haemalum and eosin and by Ehrlich's acid-haematoxylin and eosin.

"The tumour consists of masses of epithelial cells, most of which are polyhedral in shape and 12 to 15 mm. in average diameter. Each cell contains a single rounded or oval vesicular nucleus 8 or 10 mm. in diameter, usually without a distinct nucleolus. Mitotic figures are fairly numerous. The cytoplasm is finely granular or foamy, and the cell outlines in most places indistinct. The cells are arranged partly in clumps or anastomosing cords (Fig. 1a) and partly diffusely (Fig. 2a). Some of the cell clumps contain central extra-cellular vacuolated or honeycombed spaces, but nowhere are there distinct lumina of glandular character. The stroma of the tumour is not abundant, consisting of scanty strands of connective tissue between the groups of tumour cells; in many places these strands themselves contain scattered tumour cells. Blood vessels are few in number. In places there are collections of large rounded phagocytic foam-cells, lying both in the interstitial framework, and within the tumour clumps. (Fig. 3a.) These no doubt correspond with the yellow degenerate-looking areas seen on the cut surfaces of the tumour with the naked eye. The histological characters of the tumour are in accord with the clinical diagnosis of arrhenoblastoma as described by Meyer and others."

Subsequent History

The patient made a normal and uneventful convalescence, and a fortnight after the operation she was given 2 c.c. of Antuitrin S. at 3-day intervals. She menstruated normally after the fourth injection, which were then discontinued. A month later she again had a normal 4-day period. By this time, the hair on her cheeks was definitely less, but she still had a strong growth on her upper lip and chin. There was no reduction in the size of the clitoris, but her breasts were larger and tender. The areolae were brighter in colour and increased in area. There was still a strong growth of hair on the abdomen, with the same male distribution.

She has reported at 2-monthly intervals, the last being 10 months since her operation. She still has to shave, but less frequently, and there is a decided improvement in her appearance. She has less hair on her face, thighs and upper abdomen, but the male distribution has not anywhere disappeared. She has gained weight—most of this being due to an increase in the

breasts and thighs, which have now normal feminine curves. The clitoris has not changed.

She is now married to her former lover, and it is interesting to note that though she is in excellent health and full of energy, she has now a complete absence of libido. She says she has no desire and has not experienced orgasm since the operation. I had hoped she might enable me to complete the case by reporting that she had become pregnant, but unfortunately this is not so, and her husband has recently gone abroad with the Australian Imperial Force.

Discussion

The presence of a palpable abdominal tumour, which had first been noticed by the patient soon after amenorrhoea began, and which steadily increased in size, together with the obvious masculinizing syndrome, made the differential diagnosis comparatively simple in this case.

The morphology of the tumour is in appearance similar to the group termed arrhenoblastoma; and would, in Meyer's classification, conform with his third or atypical group. The pronounced masculine changes which Meyer associated with this group were present.

It is a matter of conjecture whether the rapid reappearance of the menses while she was still in hospital was due to the administration of Antuitrin S. Grant Baldwin and James Gafford in the report of their case suggest that the male hormone secreted by the tumour renders the anterior pituitrin hormones inactive either directly or indirectly. In this case, the uninvolved ovary looked so shrivelled and inactive that one would not have expected any immediate hormonal activity on its part. Possibly the extra stimulus from the injected hormone hastened its recovery.

Her earlier gratitude for the results of the operation is now somewhat tempered by the loss—temporary, I hope—of libido. I have not read of this loss in other case reports.

Summary

A case is described which is believed to be the first reported in Australia of an arrhenoblastoma of the ovary, in which typical microscopic findings were associated with a classical defeminizing and masculinizing syndrome. Since the surgical removal of this

tumour, the patient has menstruated normally and has made a gradual return to feminism.

I am indebted to Dr. R. Y. Mathew, of the Commonwealth Health Laboratory, and to my son, Flight-Lieutenant A. K. McIntyre, M.B., B.Sc. (Syd.), R.A.A.F., for assistance in the preparation of this paper. Also to Sister Tucker, of the Radiological Department of the Launceston Public Hospital, for the preparation of the photographs.

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A Case of Diabetes Insipidus in Pregnancy

BY

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THE occurrence of diabetes insipidus in pregnancy is extremely rare. In 1936 Henriet[1] could only trace 11 cases in the literature. Apart from pregnancy the disease is also infrequent. Williams,[2] for instance, reported that in nearly 2 million admissions to American hospitals the incidence was 19 per 100,000.

Briefly, this case was one of diabetes insipidus commencing at the 34th week of pregnancy. It resolved completely following premature delivery 2 weeks later. Outstanding features of the case were the onset of oedema, jaundice and secondary postpartum haemorrhage in the puerperium.

CASE REPORT

Mrs. G., aged 33, Primigravida.

There was no relevant family or medical history apart from occasional sore throats and joint pains in the hands and feet. The patient had been married for 20 months, but proper sexual intercourse had not occurred. Penetration was exceedingly painful and, according to the patient, this was due to narrowness of the vagina. When 22 weeks pregnant the patient fell heavily and fractured her clavicle. She also struck her right cheek, but the injury was slight and she did not lose consciousness, she recovered quickly and felt well until the onset of this illness.

Quite suddenly, when 34 weeks pregnant, the patient began to suffer from intense thirst and polyuria. Frequency of micturition caused severe insomnia. She became drowsy and found increasing difficulty in thinking and speaking clearly. Persistent vomiting developed which was relieved by vomiting or by taking bicarbonate of soda. Sharp pain was felt deep to the

zyphi-sternum on swallowing. Constipation was marked. In the week before admission she constantly had "spots before her eyes." Her appearance altered markedly. A dark pigmentation spread over the body. It was most marked on the face where it almost reached a bronze colour. According to her husband and doctor, during the week before admission her appearance had become old and wizened.

Physical examination. The patient was admitted in an exhausted state. Her skin was markedly dehydrated although there was slight oedema of the tibia and lower back. Desquamation of hypertrophic skin of the hands and soles of the feet was noted. Slight conjunctival jaundice was present. The heart, lungs and abdomen appeared normal. Blood-pressure 108/60. Pulse-rate 100. Temperature 98.4°F. Normal gestation, 36 weeks. The urine contained acetone but no albumin or sugar.

Nervous system. The pupils were central and circular, reacting sluggishly to light and on accommodation. The fundi were normal (the visual fields were not studied at this stage). Analysis of the cerebro-spinal fluid gave normal results. X-ray of the sella turcica and long bones was also normal. The Wassermann reaction of the blood was negative.

Progress and treatment. Intense thirst, vomiting and polyuria continued unabated for 48 hours. The patient's condition became increasingly grave. Vaginal haemorrhage accompanied by painless uterine contractions was next observed. Revealed accidental haemorrhage was diagnosed and the membranes were ruptured by catheter. Fifteen ounces of liquor amnii were withdrawn. Labour proceeded satisfactorily without appreciable loss of blood. Twenty-four hours later the os uteri was fully dilated. To avoid bearing-down efforts in the 2nd stage of labour, low forceps delivery was performed under spinal anaesthesia. The child was stillborn, although the foetal heart was heard just before delivery. The placenta was expressed by the gentle application of Crede's method. The uterus then became firm without the use of oxytocic drugs. The loss of blood was less than normal.

Post-mortem findings. The foetus weighed 6 pounds, 2 ounces. The primary cause of death was presumably asphyxia following premature separation of the placenta. There was a retro-placental clot of moderate size and recent origin. Marked bilateral hydronephrosis was present. Erythropoeiesis and haemosiderosis were excessive in the liver and spleen. Renal

tissue, however, did not show any of these features and appeared normal histologically. Blood films showed large numbers of immature red cells with macrocytosis and basophilia.

The Puerperium. The outstanding features were:

1. Cessation of the polyuria and thirst.
2. Temporary increase in jaundice.
3. Temporary increase in oedema.
4. Secondary post-partum haemorrhage.

1. *Cessation of polyuria and thirst* (see Chart 1). Twenty-four hours after delivery the urinary excretion fell from 14 to 4 pints and the intake of fluids to $4\frac{1}{2}$ pints. The grave state of the patient forbade withholding pitressin although it masked what was probably the specific curative effect of emptying the uterus.

Pituitary extract was given thus:

1st day, pitressin 4×5 units; 2nd day, 2×5 units; and on the 3rd and 4th days, 5 unit doses of pituitrin.

During the first 4 days of the puerperium repeated catheterization was necessary. The patient lost the urge to micturate and could not empty her bladder spontaneously. Urinary infection did not, however, develop. Polyuria and thirst rapidly disappeared. Seventy-four days after delivery the average output of urine was 3 pints. The specific gravity of a morning specimen was then 1018, while an average reading for 24 hours was 1024.

2. *Jaundice*. The slight conjunctival jaundice which was noted on admission spread over the body during labour. It was only of moderate degree. There was persistent heartburn, substernal pain and, occasionally, nausea and vomiting. At first the liver was not palpable. After 10 days, however, it was easily felt 3 finger-breadths below the costal margin. There was bile in the urine. The stools were normal. The Van den Bergh reaction was strongly positive direct. The icteric index was 50. The fragility of the blood was normal.

Ten cubic centimetres of calcium gluconate were given intravenously for 4 days with abundant oral glucose. The jaundice gradually improved and disappeared 14 days after delivery. The urine did not contain any bile after the 14th day, but the liver was still enlarged on the 22nd day. On the 74th day, however, the liver was no longer palpable. The icteric index at this date was 5.

(It is relevant to note, under this heading, that distension of the bowel was not observed until the 11th day. A flatus enema was sufficient to relieve the condition.)

3. *Oedema.* Slight oedema was present over the legs and back for 2 days before delivery. In the puerperium it became fairly marked and generalized. The oedema (over the body in particular) was of brawny consistence and pitted only after prolonged pressure.

Blood-urea readings are given on Chart 2. The highest, 102 mgm., was recorded on the 5th day, but it must be noted that the loss of blood and blood transfusion preceded this. The urine contained traces of albumin for 25 days after delivery, after which abnormal constituents were not found. The specific gravity of the urine returned to normal.

On the hypothesis that there might be a degree of hypofunction of the thyroid and suprarenal glands thyroxine gr. 1/60th with eucortone 1 c.c. were injected, on the 5th, 6th and 7th days. Oedema diminished thereafter and was absent by the 14th day. It seems improbable, however, that this treatment was responsible for the improvement.

4. *Post-partum haemorrhage.* Despite the satisfactory uterine activity in labour, bleeding occurred from the vagina for 3 days after delivery. The loss of blood was not excessive. The haemoglobin level, however, fell from 60 per cent to 45 per cent. On the 3rd night, following gentle expression of some vaginal clots, the patient suddenly collapsed. Her pulse-rate became rapid and her skin cold. She did not lose consciousness, however, and recovered quickly after treatment with a shock-cradle and transfusion with 600 c.c. of blood. There was no further bleeding and the uterus commenced to involute satisfactorily.

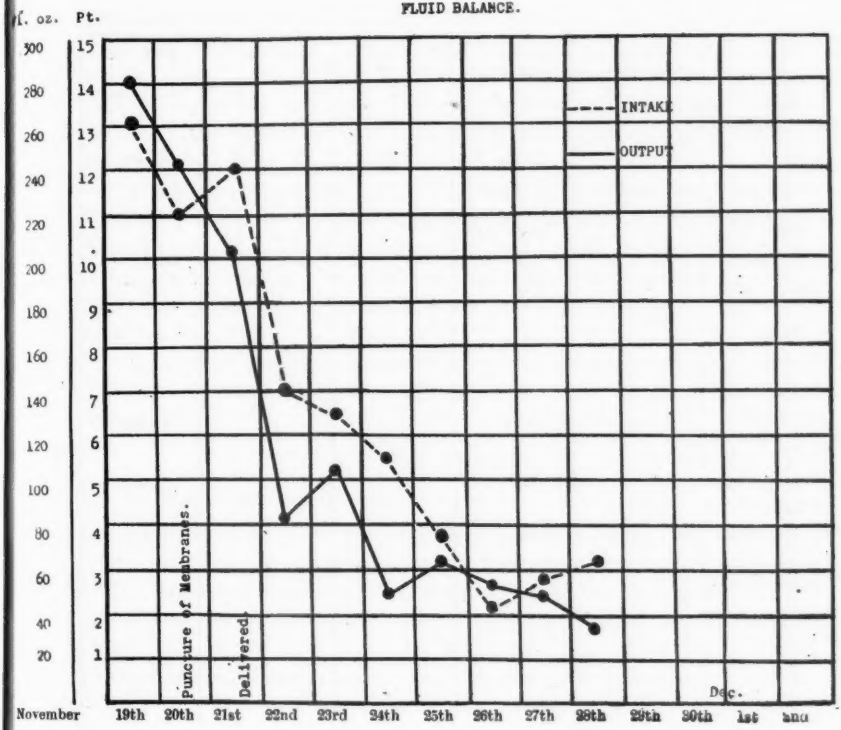
Biochemical findings (see Chart 2). The maintenance of normal chloride levels in the urine, blood, cerebro-spinal fluid and liquor amnii is remarkable in view of the large amount of fluid-exchange. It is, however, a usual finding in diabetes insipidus. The confirmatory positive Van der Bergh reaction with an icteric index of 50 is also noteworthy. The blood-urea levels are difficult to assess in this case owing to the occurrence of haemorrhage and the necessity for blood transfusion.

Blood picture. In brief: 1st day of puerperium red blood corpuscles 3.08 millions, white blood corpuscles 4,100. Haemoglobin 60 per cent, colour index 96. Differential count normal.

7th day (transfusion on the 3rd day): red blood corpuscles 2.3 millions, white blood corpuscles 10,900. Haemoglobin 48 per cent, reticulocytes 11 per cent, platelets 247,500. Only a very occasional normoblast was observed. The condition of

CHART I.

FLUID BALANCE.



H. MC.L.

CHART II.

BIOCHEMICAL FINDINGS.

	Day before Delivery.	Day of Delivery.	5th. Day.	7th. Day.	74th. Day.
BLOOD.					
Chlorides.		614 mg. %		584 mg. %	614 mg. %
Urea.	41 mg. %	53 mg. %	102 mg. %	78 mg. %	23 mg. %
Sugar.	85 mg. %	72 mg. %			
CO_2 Combining Power.		43.5 vol.%			
V. D. Bergh.		+ Direct.		+ Biphasic.	Negative.
Icteric Index.		50.		50.	5.
URINE.					
Albumin.		Trace.	Trace.	Nil.	Nil.
Acetone.	+	+	—	Nil.	Nil.
Chlorides.		29 mg. %			35 mg. %
Bile.	—		++		
Spec. Grav.	1002.	1004.			1008.
C.S.F.					
Total Albumin.		20 mg. %			
Chlorides.		730 mg. %			
LIQUOR AMNII.					
Chlorides.		614 mg. %			

H. MC.I.

mycrocytic anaemia was diagnosed. Iron therapy was sufficient to cure the condition.

Other findings. The patient recovered gradually, but she was still very weak on dismissal 22 days after delivery. She sweated profusely during convalescence and especially at night. She remained very drowsy for 10 days, although her mental function was normal by the 4th day. This condition of torpor resolved satisfactorily 14 days after delivery.

Further findings. The patient regained her normal pleasant appearance 8 weeks after discharge. She complained of cramp-like pains in the calves of her legs and occasional mild headaches. Her vision became blurred if she read for more than a few minutes.

A full examination which included visual fields and acuity, X-ray of sella turcica and long bones, biochemical analysis and blood-count disclosed nothing abnormal. The urinary output averaged 3 pints. It did not contain any abnormal constituent. The specific gravity of a morning specimen was 1018 and of a 24-hour specimen 1024.

Menstruation had commenced. Pelvic examination gave normal results and premenstrual endometrial biopsy was also normal.

Discussion

A. Experimental Work.

At present Ranson's views on the aetiology of diabetes insipidus are widely accepted, viz., "that the disease is essentially a hypophyseal deficiency syndrome caused by a diminution or total absence of the anti-diuretic hormone of the neural (posterior) lobe when the latter is extirpated or becomes atrophic secondary to interruption of the supra-optico-hypophyseal tracts".[3] The posterior lobe of the pituitary gland can be described as a large ganglion in which terminate many nerve fibres related to the hypothalamus.[5] This ganglion secretes (among other hormones) the anti-diuretic factor. According to Magoun,[4] this hormone is also secreted by the identical tissue of the infundibular stalk and median eminence. Deficiency of the hormone leads to diabetes insipidus, provided the anterior lobe of the pituitary gland is functioning properly.

Recent experimental work, moreover, points to the fact that the anterior lobe of the pituitary gland secretes a diuretic hormone. Barnes,[6] Biasotti,[7] and Teel[8] fed dogs with anterior lobe extract and produced diuresis. Barnes performed thyroidec-

tomy and cured the experimental diabetes. On the other hand, feeding these thyroidectomized dogs with thyroid gland reproduced the disease. Barnes concluded, therefore, that the anterior lobe acted indirectly through the thyroid gland to produce diuresis. Further work on dogs by Mahoney and Sheehan[9] tends to support this view. Alexander and Biggart,[10] moreover, showed the importance of the thyroid in producing diabetes insipidus experimentally in dogs. These workers brought about a cure of experimental diabetes by removing the thyroid gland. In another experiment removal of the pancreas brought about the same result.

In conclusion, therefore, recent experimental work explains diabetes insipidus as a disease caused by a deficiency of the anti-diuretic hormone in the presence of an intact anterior lobe. It seems likely that the anterior lobe has a diuretic action, although this function is possibly indirect, i.e. through its action on other glands in the hormonic system.

B. Clinical Aspects of the Case.

There are many predisposing factors which can lead to deficiency of the anti-diuretic hormone.[11] In this case it is not possible to rule out trauma although it seems unlikely in view of the mildness of injury. Pregnancy appears to have been the main predisposing factor.

Anselmino and Hoffman[12] describe a case of diabetes insipidus which recurred in two successive pregnancies. They noted that the disease improved at the time when the Zondek-Aschheim reaction of the urine became negative, and reasoned that the negative reaction indicated diminished anterior lobe activity. This resulted in the reduction of the diuretic hormone so that it could be balanced by the formerly inadequate anti-diuretic hormone. Such a theory might explain the case of Fruinsholtz,[13] or even our case. There are, however, several cases in the literature in which the clinical picture is entirely different. These cases are not easily explained. Duvoir's[14] patient, for instance, had diabetes insipidus for 17 years. She became pregnant on three occasions, and on each occasion the disease improved, but returned again in the puerperium. Artaud's[18] case, on the other hand, had diabetes insipidus which temporarily became worse during pregnancy.

In view of these reports it is obvious that a common aetiological factor cannot be named to explain the various clinical manifestations of the disease in association with pregnancy.

The cause of the post-partum bleeding in our case is doubtful. As is usually the case in diabetes insipidus, labour was normal. The placenta was expressed with ease and the loss of blood was less than usual. It is conceivable, however, that the secondary bleeding was a result of temporary deficiency of the oxytocic factor of the posterior lobe. Ranson's work raises the possibility of a co-existing deficiency of the anti-diuretic and oxytocic factors. In one of his experiments, 8 cats became pregnant following the production of diabetes insipidus. In all the cases labour was complicated by severe uterine inertia. On the other hand, Robson believes that the "active changes occurring at parturition and leading to the expulsion of the foetus and placenta may take place in the absence of the pituitary (both anterior and posterior lobes)."[17] At present, therefore, there is experimental evidence of contradictory nature.

Diabetes insipidus with pregnancy has so far not been reported in association with uterine inertia. (Fruinsholtz has reported a case in which diabetes insipidus co-existed with the delivery of a very large child. In this case delivery was carried out by the forceps after prolonged labour.) Haemorrhage in our case was of doubtful origin but the possibility of temporary deficiency of the oxytocic factor seems to exist as an aetiological factor.

Oedema was noted by Lévy-Solal,[15] in a case of diabetes insipidus with a pregnancy mole. Dreyfus,[16] in his classic monograph, does not make any mention of it and it must be exceedingly rare. Oedema is difficult to explain in our case, unless simply as further evidence of water imbalance.

Jaundice in the puerperium is difficult to correlate with diabetes insipidus. Its appearance may have been coincidental. Similar manifestations were not encountered in the literature.

Other interesting features of the case such as torpor, dyspepsia and paradoxical sweating, are apparently rare features in diabetes insipidus.

Future treatment. Recurrent (transient) diabetes insipidus has been reported in the literature, yet it is difficult to be sure that the disease would recur if our patient again became pregnant.

Our patient desires another child but for the next 6 months contraceptive measures are being practised. After this period a full medical examination will be carried out. If it is then decided to allow a pregnancy, the earliest sign of polyuria would

be an indication for the performance of hysterotomy and sterilization.

Summary

A case of transitory diabetes insipidus in pregnancy is reported and the literature reviewed.

Acknowledgment

Our thanks are due to Professor Dugald Baird for permission to publish a report of this case and for his helpful criticism and advice. We are also grateful to Dr. A. M. Lyall, of the Department of Biochemistry, for his assistance in the investigation and treatment of the case and to Dr. W. Wyness Nicoll, of Inverurie, Aberdeenshire, for much valuable data.

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Superinvolution of the Uterus following Intra-partum Infection with Gas-forming Organisms

BY

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INFECTION of the uterine contents becoming established before delivery greatly increases the risk to mother and baby, and especially if the organism responsible is one of the gas-producing anaerobes. Although such cases are uncommon, the maternal risk is very high, and the foetal mortality in our experience has been one hundred per cent. If the mother survives the immediate risks of labour and the puerperium, however, there is one late complication which seems especially liable to follow this type of infection, and that is the occurrence of superinvolution of the uterus. As the importance of infection with gas-forming organisms in the aetiology of this condition does not seem to be generally realized, we have thought it worth while to report the details of 3 cases which we have observed at Walton Hospital.

CASE 1. Mrs. E. C. Primigravida. Aged 23. Normal pregnancy. Labour commenced at 1 A.M. on August 15, 1938, the expected date of delivery, and patient was admitted to hospital at 9.15 A.M. the same day. The membranes ruptured immediately after admission, and the liquor was noted as being meconium-stained. The head was starting to engage in the pelvis, and the foetal heart was regular. The baby was noted as being large, but an X-ray examination during labour showed a normal foetus. Labour continued slowly, and it was found on vaginal examination on August 17 at 11.30 A.M. that the cervix was fully dilated and the liquor offensive. This was the only vaginal examination carried out before delivery. At 5 P.M. the same day the temperature was 100.4°F., pulse-rate 128, and the foetal heart still present. At 8.15 P.M. the foetal heart could not be heard. At 11.30 P.M. there was a very offensive dis-

charge from the vulva with gas, and crepitation could be felt on palpation of the uterus. Sulphonamide was given by mouth in the later stages of labour. Under general anaesthesia the head was perforated and delivered with volsellae. Great difficulty was found in delivering the shoulders, and one clavicle was divided. The placenta separated normally. There were slight lacerations of the perineum which were repaired. The patient did not show signs of shock. Culture of the uterine contents made at the time of delivery failed to show *Cl.* welchii. The foetus weighed $8\frac{1}{4}$ pounds without the brain tissue. Post-mortem examination of it showed that both lungs were expanded and floated in water, and that both the lower femoral and upper tibial epiphyses were present. The puerperium was complicated by the continuance of local uterine sepsis and double white-leg, but the patient was discharged well on September 20, 1938.

Her general health remained good, but menstruation did not commence. Accordingly she was admitted to hospital and examined on October 16, 1939. Bimanual examination then showed a very tiny uterus, and the sound only passed into the external os for 2 inches. An attempt was made to inject lipiodol into the uterus, but this failed, and the X-ray picture taken showed that none had passed beyond the tip of the cannula. An attempt was also made to obtain endometrium for section, but failed. The patient has remained in good health, and coitus is normal. There has been a gain of 21 pounds in weight, but in spite of treatment with numerous glandular preparations, menstruation had not commenced up to March, 1941.

CASE 2. Mrs. L. W. Primigravida. Aged 23. Patient was admitted as an emergency case on April 18, 1939, after having been in labour for 2 days. The forceps had been applied unsuccessfully before admission. On examination the head of the child could still be felt on abdominal palpation, the foetal heart was present, the cervix was oedematous and only half dilated, and the vagina was lacerated. Sedative drugs were given, and labour proceeded slowly. At 9.30 A.M. on the 19th, the foetal heart could not be heard, the uterus was tympanitic, the cervix fully dilated, and the head still high. Perforation of the head was carried out, and volsellae applied. There was little further advance, and at 12.15 A.M. the following day, delivery was completed by the forceps, a cleidotomy also being carried out. Gas was present in the uterus, and culture of the contents showed *b.* coli and non-haemolytic streptococci, but *Cl.* welchii was not

found. The foetus weighed 9½ pounds without brain tissue. Prontosil soluble and anti-gas-gangrene serum were given. Convalescence was stormy, and when the patient was discharged on July 24, there was a vesico-vaginal fistula. This was closed by operations on October 13, 1939, and February 19, 1940. Up to June 21, 1940, the patient had not menstruated. An examination under anaesthesia was carried out on that date. The fistula was soundly healed. The uterus was very tiny, and a uterine cavity could not be found.

CASE 3. Mrs. R. M. Primigravida. Aged 27. This patient was admitted to hospital since delivery by the forceps had failed on March 7, 1939. On admission the patient was shocked, the vulva oedematous, the vagina lacerated, the cervix three-quarters dilated, and the head still high and with a large caput. The foetal heart could not be heard. At 6 P.M. the head was perforated. The following morning at 9 A.M. the uterus was found to be tense and tender. The condition of tonic contraction was diagnosed, and a lower segment Caesarean section was performed under general anaesthesia. The uterine contents were very offensive, and gas was present, but unfortunately a culture was not made. A distended foetus weighing 8 pounds was extracted with difficulty. The placenta was left *in situ* and expelled the following morning through the vagina. Anti-gas-gangrene serum was given. The convalescence was stormy, and sloughs were passed vaginally. The patient was discharged on May 11. Menstruation recommenced, but ceased in December, 1939. In June and July, 1940, there were slight periods, and in August, a watery discharge for 3 days. On October 28 the patient was examined under anaesthesia. The vaginal vault was found to be fibrosed, and the uterus very small. The cervix was stenosed, and, though with difficulty a probe passed some way through a small opening in the vaginal vault, it was not thought that this had passed into the uterine cavity. The patient has gained weight, and is otherwise well.

The records of three further cases in which there was a gas infection during labour have been consulted. In the first, menstruation recommenced normally, and the patient has recently become pregnant again after 3 years. In the second, menstruation had not recommenced up to 2½ months after her discharge, and since then the patient has not been seen. The third patient had one subsequent delivery, which was complicated by an adherent placenta requiring manual removal. In each case the foetus was stillborn.

Discussion

Cases of infection with gas-forming organisms are uncommon in labour and the puerperium. It would thus seem that the risk of superinvolution following this type of infection is very great, as we have not met with any similar cases following infection with other organisms among the very large number of cases of puerperal and post-abortum infection which have passed through our hands in Walton Hospital during the last 5 years.

The presence of gas will always raise the suspicion of infection with *Cl.* welchii, but in the 2 cases in which cultures were made, this organism was not found. It is possible that many of these infections are due to anaerobic streptococci. Colebrook[1] has shown in a review of puerperal infections due to these organisms that many strains produce gas in culture, and that they are difficult to isolate by the usual routine methods.

Atrophy of the uterus with amenorrhoea following confinement has long been recognized under the name of "superinvolution." Some of these cases come under the heading of Simmond's disease, which is an endocrine disturbance which Sheehan and Murdoch[2] have shown to be due to necrosis of the anterior pituitary following shock in labour. In the cases reported above, a severe inflammation due to gas-forming organisms seems to have caused destruction of the mucous membrane of the uterus and obliteration of the uterine cavity. Shock was a feature in only one case, and general endocrine symptoms, apart from gain of weight, were not prominent in the subsequent histories. In Simmond's disease, on the other hand, the anatomical changes may not be gross, and in one such case which we have investigated and in which amenorrhoea followed extreme shock in labour, lipiodol was found to enter the uterine cavity and Fallopian tubes. Sheehan and Murdoch[3] have pointed out that if genital atrophy has not taken place, a further pregnancy may occur, and may indeed cure the disease. In the cases described above, it is obvious that further pregnancy is impossible.

These cases are very tragic, when we consider the high foetal mortality and the impossibility of further pregnancy. Every effort must be made, therefore, to prevent the occurrence of gas infection in labour. The factors predisposing to this kind of infection are similar to those responsible in the injuries of war and road accidents. Thus we find that improper interference with laceration, such as occurs when delivery by the forceps has

failed, intra-uterine death of the foetus, and actual injury to the foetus itself, are important factors. Browne[4] has reported 2 cases of *Cl.* welchii infection following the application of Willett's forceps to the foetal scalp in the treatment of placenta praevia. In the first of our present cases, however, there was neither examination nor interference till late in labour, and it would appear that if intra-uterine death of the foetus occurs for any reason after rupture of the membranes, there is a risk of infection with gas-forming organisms of endogenous origin occurring, especially if the foetus is a big one.

Some of the factors that increase the risk of this type of infection, such as a large foetus, early rupture of the membranes, slow dilatation of the cervix, and interference, are especially likely to be found in the condition described by De Lee[5] under the name "dystrophia dystocia syndrome." In an investigation of 62 cases of this syndrome recently made by one of us, there were found to be 2 cases of gas infection, as well as many others in which there was a gross intra-partum infection of other types.

It is possible that in the future, especially with war experience, chemotherapy may help in the prevention of these infections, but so far our experience with the new drugs when used for the prophylaxis of this type of infection has been disappointing. If there is definite evidence after rupture of the membranes of an early intra-partum infection, and it seems likely that the progress of labour will be slow, a lower segment Caesarean section should be performed, as we now know this to have a very low risk from sepsis in such cases. Once a gross infection has become established, however, especially with gas formation, the risks of abdominal delivery are high. Vaginal delivery on the other hand, by a destructive operation in these cases, may be difficult and time-consuming, and also carries a high risk from shock and lacerations. The risks in such cases of each route must be carefully balanced. Greater hopes in the future must be placed in prophylaxis, however, and with improved obstetrics, these tragic cases should become extremely rare.

SUMMARY

Three cases of superinvolution of the uterus following infection during labour with gas-forming organisms are described, and the aetiology and prevention of this condition are discussed.

We are indebted to Dr. H. MacWilliam, Medical Superintendent, and Mr. St. George Wilson, Consulting Obstetrician and

Gynaecologist, Walton Hospital, for permission to report these cases.

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The Categories of Abortion and Abortion-Stillbirth Sequences

BY

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THE object of the present paper is to formulate the conditions under which abortion sequences and abortion-stillbirth sequences occur. These sequences, like single abortions and stillbirths, can be the end-result of various conditions, and they can in consequence be divided up into various categories, each category calling for special treatment and carrying a characteristic prognosis. Too often these cases are grouped together as instances of what is called habitual abortion and this confusion of categories leads to further confusion when the results of any special treatment are being examined.

In undertaking such a formulation it is necessary to consider not only pure abortion sequences, but also abortion-stillbirth sequences, i.e., cases in which one or more abortions are followed by, or intercalated with, stillbirths or premature births. Stillbirths and premature births must be included because they often are due to the same causes as abortion. Their exclusion from the scope of the inquiry would make the problem seem clearer, but such a clarification would be artificial because it would not conform closely to clinical experience, though in an initial investigation of the various factors concerned it would have a value.

One very real difficulty met with in investigating cases of sequential abortion is that in many, if not most instances, the immediate cause of the abortions cannot be discovered, or may not become apparent for some time, perhaps not until the patient has finished her reproductive career. A second difficulty is that many of these cases have a multiple causation, so that they cannot be allocated exclusively to one particular category.

Apart from direct experimental evidence all that can be done to overcome these difficulties is to watch each case over a period

of years, and then to use any abnormal factor which may be observed in each case to allocate it to its proper category. For instance, chronic nephritis is one very obvious abnormal factor which serves to characterize many abortion sequences.

During the inquiry 69 cases were investigated. A selection was not made apart from excluding a few cases, perhaps a dozen in all, in which it seemed pretty certain that the abortions were self-induced. None of the patients in the series was given any treatment other than general measures in the pregnancy in which they came under observation, although most of them had had various specific treatments in previous pregnancies. All that was done was to enjoin rest and to treat any abnormal conditions as they arose and were diagnosed. The series may thus be regarded as an unselected and untreated group of abortion and abortion-stillbirth sequences. It is not claimed that it contains examples of every type of abortion sequence that can occur; for instance, it does not include any cases of repeated abortion following high amputation of the cervix, but it may fairly be claimed that the series does include most of the abortion sequences commonly met with in practice.

When the cases had been collected it became quite clear that they could be divided into two major groups. In the first group, numbering 22, a cause, immediate or remote, could not be found for the chain of abortions. In the second group, numbering 47, some cause or some associated abnormal factor could be found.

Abortion and Abortion-Stillbirth Sequences without any Discernible Cause.

These women had a run of abortions, or abortions and stillbirths, for which a cause could not be found. They appeared perfectly healthy, did not develop any signs of disease during their pregnancies, made complete recoveries, and had a normal family history. Renal function tests were normal and the Wassermann reactions were negative.

The only positive fact that emerged from a consideration of these cases was that in every instance a live child was ultimately born without any treatment whatever. The probable explanation is that these sequences are instances of the chance incidence in successive pregnancies of some of the casual or non-recurrent causes of abortion. If this is the right interpretation, then this high spontaneous cure-rate is only what would be expected.

This aspect of the problem has been discussed in a previous

paper in which it was shown on theoretical grounds that random factors can be responsible for an abortion sequence, and that in consequence a high spontaneous cure-rate for abortion sequences as a whole is to be expected, ranging from a 68 per cent chance of a woman who has had 2 abortions carrying a 3rd pregnancy to a live birth to a chance of a woman with 4 abortions having a live baby from her 5th pregnancy.

The statistical aspects of the problem have since been examined by MacGregor and Stewart,[1] by Bacharach,[2] and by the Council on Pharmacy and Chemistry of the American Medical Association.[3] These authors have criticized the theory and modified it, without, however, disputing its general premises. A discussion of these criticisms is given in an appendix to the present paper, not with any desire to evade them, or to minimize the importance of the statistical aspects of the problem, but because a statistical analysis does tend to confuse or overshadow the more important clinical study of individual cases. There is a limit to the value of statistics when applied to any confused aggregate of data, and the problem of recurrent abortion with its medley of possible causes is a good example of both the value and the limitations of the statistical method. On the one hand, a statistical examination can be used with value to criticize any original assumptions and claims of successful treatment. On the other hand, it can give an unreal appearance of uniformity to a heterogeneous group. After the statistical method has made its original contribution to a problem then it must wait until all the data are collected and measured before it can profitably be used again. A quotation from Whitehead's book "Science and the Modern World" puts the point more clearly: "So far are statistical averages from throwing light on the ultimate nature of things, that they blur and obliterate the individual characters of the individual organisms. If we wish to throw light upon the facts relating to organisms, we must study either the individual molecules and electrons, or the individual living beings." The fact that abortion sequences are a confused group imposes a strict limitation to the value of a mathematical treatment which is based on the premise that they form a homogeneous group. In this special case the immediate value of a statistical examination is that it demonstrates that any series of abortion sequences is weighted by cases in which the non-recurrent causes of abortion are responsible for the sequence.

To sum up the foregoing, the first category of abortion

sequences that can be isolated from the whole group is that category comprising the cases for which a cause cannot be found. The isolation of this category is of value in two respects. In the first place it enables a definite prognosis to be given to some of these patients. In the second place it entails the necessity for excluding cases for which a cause cannot be found from any series of abortion sequences when the results of a particular form of treatment are being considered. While this may take away some of the pride experienced in bringing these cases to a successful conclusion it may provide an answer to cases which do not go so well, illustrated by a remark by Benvenuto Cellini: "They were married for eighteen years, always greatly desiring to be blessed with children. At the end of this time the wife miscarried of two boys through the unskilfulness of the doctor. Later on she had a living child."

CASE DETAILS OF SEQUENCES WITHOUT ANY DISCERNIBLE CAUSE. 22 CASES.

No.	Fraternity in Order of Birth
44.	Abortion 22 weeks; abortion 20 weeks; live.
48.	Abortion 12 weeks; abortion 12 weeks; live.
4.	Abortion 14 weeks; abortion 12 weeks; live; live.
37.	Abortion 10 weeks; abortion 10 weeks; live; abortion; live; live.
57.	Abortion 8 weeks; abortion 12 weeks; live.
78.	Abortion 8 weeks; abortion 12 weeks; live.
74.	Premature; abortion; live.
68.	Premature; abortion; abortion; live; live.
63.	Live; abortion; abortion; live.
16.	Live; abortion; abortion; live; live.
79.	Live; abortion; abortion; live.
51.	Live; abortion 12 weeks; abortion 12 weeks; live.
73.	Live; stillbirth; abortion; premature; live; live; live; live; live; abortion; abortion; live.
46.	Abortion; live; abortion; live.
67.	Live; live; live; live; abortion; abortion; live.
36.	Abortion 8 weeks; abortion 8 weeks; abortion 10 weeks; live.
6A.	Premature; abortion; abortion; abortion; abortion; abortion; abortion; live; live; live.
40.	Live; live; live; abortion 12 weeks; abortion; abortion; live; live.
2.	Live; abortion; abortion; abortion; live.
6.	Live; live; live; live; abortion; live; abortion; live.
70.	Live; abortion 10 weeks; abortion 14 weeks; stillbirth; stillbirth; live.

Abortion and Abortion-Stillbirth Sequences with a Discernible Cause.

In the second major division of the cases some abnormal factor could be found to which the sequence might be attributed. These abnormal factors were as follows:

1. Toxaemia of pregnancy, nephritis, hypertension.
2. Heart disease.
3. Nutritional and endocrine faults.
4. Bad family history.
5. Malformations.

Toxaemia of pregnancy, nephritis, hypertension. Inveterate aborters often belong to this group. These conditions may be occult and the first abortion may be the first sign that there is anything wrong, and often from the patient's point of view the only sign. For this reason a renal investigation is indicated in every abortion sequence.

The cases in the series include instances of primary toxaemia, chronic nephritis and essential hypertension. One important point in the diagnosis of abortion sequences belonging to this category is that in some of the patients there may be no evidences of toxaemia or renal failure evident in the pregnancies which end in abortion, the signs of toxaemia only appearing in those pregnancies which continue nearer to term. The number of cases in the series does not justify separate examination of the toxaemia, nephritis and hypertension cases, although these various conditions do not all carry the same risk to the foetus. There is for instance a great difference between the chances of a woman with a definite nephritis and objective cardiovascular lesions having a live baby and those of a woman who has only had a transient mild albuminuria with apparent complete recovery.

If the group as a whole be compared with the group in which a discernible cause could not be found it is noticeable how the abortions tend to occur later in pregnancy. As pregnancy proceeds, while the embryo becomes less sensitive to the various accidental external causes which cause abortion, it becomes more sensitive to changes in its internal environment, because its increasing size makes it more dependent on the amount and quality of the blood reaching the placental site.

Perhaps the most interesting cases in the group were those patients with hypertension. Often there is no other symptom or abnormal physical sign to be found. The patient feels and looks

perfectly well but may nevertheless abort with regularity, and even the most careful management may fail to secure a living child.

While the prognosis of the whole group is poor, a number of these patients do have living children. Of the 18 women in the group 11 had a living child at one time or other, and out of a total of 39 pregnancies 17 live children were born.

ALBUMINURIA, TOXAEMIA OF PREGNANCY, NEPHRITIS, HYPERTENSION. 18 CASES.

WITHOUT ANY OTHER ASSOCIATED FACTOR. 4 CASES.

No.	Fraternity in Order of Birth	Remarks
20.	Abortion; live; abortion; abortion; live	Toxaemia 2nd.
31.	Abortion; stillbirth; live; live	Albuminuria 2nd.
41A.	Abortion; abortion; stillbirth	Albuminuria 3rd.
55.	Abortion 2 months; abortion 2 months; abortion 4 months	Hypertension in all 3 pregnancies starting 8th week.

WITH SOME OTHER ASSOCIATED FACTOR. 14 CASES.

No.	Fraternity in Order of Birth	Remarks
15A.	Live; abortion 22 weeks; abortion 22 weeks	Hypertension at 8th week. Patient's mother in asylum.
16A.	Live; live; abortion; live; abortion; abortion	Bad general condition.
47.	Abortion 20 weeks; stillbirth; live (premature); live; live; stillbirth	Accidental haemorrhage, 6th. Bad general condition.
64.	Live; live; abortion 10 weeks; abortion 22 weeks; live; twins; stillbirth	Chronic nephritis.
1.	Stillbirth; abortion 12 weeks; live	Bad family history.
3.	Abortion 22 weeks; stillbirth; abortion 24 weeks	Bad family history.
25.	Abortion 10 weeks; live (4½ pounds); abortion 12 weeks; live	Bad family history.
34.	Live; stillbirth; abortion; live	Bad family history.
35.	Stillbirth; abortion	Mother died eclampsia.
75.	Abortion 14 weeks; premature 7 months; premature stillbirth; live	Bad family history.
38.	Abortion 28 weeks; abortion 12 weeks; live	Bad family history.

This aspect of the problem has been examined by Browne and Dodds,[4] who consider that the infant salvage rate varies around 87 per cent in pre-eclamptic toxaemia, 80 per cent in recurrent toxaemia, 63 per cent in chronic nephritis and 52 per cent in eclampsia. These authors were, however, mainly concerned with the chances of a live birth after viability has been reached. The history of one or more previous abortions in a woman with a toxaemia indicates a proportionately severer lesion, and makes the prognosis for subsequent pregnancies worse. In the present series the prognosis appeared better if the woman had already carried one child past the period of viability. The first pregnancy indeed may represent these patients' best chance of a living child, and most obstetricians stress the value of the most conservative treatment possible of a toxaemia appearing in a first pregnancy. Rest and protection from strain and infection will often enable these pregnancies to continue until the child is viable and it is often advisable to hospitalize these women for the greater part of their pregnancies.

Heart disease. There were only 3 cases in this group. This accords with the clinical experience that women with heart disease do not usually abort and it seems significant that in each one of these 3 cases secondary pulmonary lesions were present, in one a severe chronic bronchitis and asthma, in the other 2, pulmonary fibrosis associated with clubbed fingers. In heart

HEART DISEASE. 3 CASES.

No.	Fraternity in Order of Birth	Remarks
3.	Abortion; stillbirth; stillbirth; live; abortion	Rheumatic mitral lesion, secondary chronic bronchitis.
34.	Premature; abortion; abortion; abortion; abortion; live	Hypertrophied heart due to bronchiectasis following pneumonia; cyanosed, clubbed fingers.
62.	Premature; premature; abortion; abortion; premature; live	Congenital pulmonary stenosis, cyanosis, clubbed fingers. In hospital 6 months last pregnancy. Caught cerebrospinal meningitis at 38th week and died. Post-mortem Caesarean section, living normal child.

disease with a secondary pulmonary lesion there is a special load on the peripheral circulation. The abortions are ascribable to a combination of anoxaemia and stasis in the blood sinuses. Foetal blood with its different cell-picture and its special oxygen dissociation rate would appear to compensate the milder peripheral anoxaemia of an uncomplicated mitral lesion.

Nutritional and endocrine faults. To this category were allocated 18 cases in which some nutritional or endocrine lesion was found. The category is certainly compound, and in any more extensive series of abortion sequences it could be subdivided. It may be argued that subjective judgment forms too large a part in the detection of such faults. On the other hand, subjective judgment is the only instrument available in a large number of clinical problems such as the present one.

The cases in this category can be divided into two contrasting groups, one in which the patients were too fat, and one in which they exhibited a poor general nutritional state, and what may be called a "poor pregnancy response."

Obesity. Taking the obesity group first, there were 7 patients in whom obesity was found associated with an abortion sequence. In 2 or 3 cases the general build of the patient suggested some dispituitarism. It is likely the whole group is a compound of various conditions. The prognosis appears to be good; it will be noted that in every case a spontaneous cure resulted. The fraternities all started with abortions, not as some of the toxaemic group did, with live births.

OBESITY ASSOCIATED WITH ABORTION SEQUENCES. 7 CASES.

No.	Fraternity in Order of Birth	Remarks
22.	Abortion 24 weeks; abortion 24 weeks; live	? Hyperpituitary type.
8.	Abortion 16 weeks; abortion 16 weeks; live; live	
17.	Abortion; twins (premature); live	
30.	Abortion 16 weeks; stillbirth (premature); live	Hyperpituitary type.
26.	Abortion; abortion; live.	
59A.	Abortion; abortion; abortion; abortion; abortion 24 weeks; live	No treatment in successful pregnancy.
80.	Stillbirth (premature); abortion; live; live; live	

Bad general condition and poor pregnancy response. The second sub-group in this category included 11 cases, and this sub-group too is certainly compound. Three of the patients had a definite thyroid lesion. The other patients were in poor general health, or of poor physique, underweight, thin, nervous. They tolerated their pregnancies badly, hyperemesis was troublesome, and the patients never felt well during pregnancy. The live children that were born tended to be undersized. On the whole prognosis appears to be fair except where definite evidence of thyrotoxicosis is present.

No.	Fraternity in Order of Birth	Remarks
13.	Abortion 10 weeks; abortion 14 weeks	Undersized, thin, nervous, morning sickness bad.
49.	Live, 5 pounds; live, 7 pounds; live, 5 pounds; stillbirth, 3 pounds; abortion; abortion; abortion; abortion; live; 5 pounds	Apparently healthy woman. Living children underweight.
56.	Abortion 24 weeks; abortion 20 weeks; live	Thin, nervous, underweight, history of " nervous breakdown " at 17.
60.	Male, 4½ pounds; abortion 10 weeks; abortion 10 weeks; abortion 10 weeks; live; 8½ pounds; live	Poor general condition.
10A.	Abortion 12 weeks; abortion 11 weeks; live	Thin, nervous; small diffuse goitre since age 9.
53.	Abortion; stillbirth (premature); live; live	Poor general condition. Undersized.
81.	Live; live; live; live; abortion; abortion; premature	Thin, pale, nervous. Bad family history.
54.	Abortion 6 weeks; abortion 12 weeks	Exophthalmic goitre, thin, nervous, tachycardis.
74.	Abortion 18 weeks; abortion; abortion 14 weeks	Pale, thin, weak. Patient is 14th child.
32A.	Live; stillbirth; abortion; abortion; premature; live; live	Pale, thin, worried; diffuse thyroid swelling.
87.	Abortion; premature; abortion; abortion	Progressive exophthalmic goitre; thyroidectomy between 2nd and 3rd pregnancy with some relief.

Bad family history. In 2 cases all that could be found wrong with the patients was a suspicious family history. Were it not for the fact that a bad family history was noted in many cases in the other categories, these two cases would have been put into the "no evident cause" group. However, it seems likely that the family history is of importance as evidence of a latent poor reproductive physique.

The details of these 2 cases are as follows:

No.	Fraternity in Order of Birth	Remarks
84.	Abortion; abortion; abortion	Patient looks well. Mother died 54, father died 54. One sister died meningitis age 17. One brother well, one brother died in infancy.
19.	Live; live; premature stillbirth; abortion 24 weeks; abortion 19 weeks	Father died 50 (alcohol). Mother well. She had 16 children, only 5 surviving to adult life.

A bad family history is not an immediate factor leading to a sequence of abortions. In so far as it is concerned it operates by producing maternal faults which in turn lead to the abortions.

In the whole series the family history was available in 40 cases. It was considered bad in 20 instances, divisible up as follows:

A. Familial cardio-renal disease, 7 cases.

B. Poor familial physique, premature deaths of parents, 8 cases.

C. Alcoholism in both parents, 2 cases.

D. High incidence of abortion in family, 1 case.

E. Hereditary nervous disease, 2 cases.

In 18 of these 20 patients with a bad family history there was some other abortion-determining factor present so that it was possible to allocate them to various other categories. In the 2 cases just described, Nos. 84 and 19, no other abnormal factor could be found.

Group B, the "poor familial physique and premature death of parents" group, is the only group that perhaps calls for any

illustration. Details of two of the cases in this group are as follows:

CASE NO. 1.

Father died of pneumonia aged 48; mother died of cancer aged 38. One sister died puerperal fever, second sister one abortion and one living child. One sister unmarried, well. No brothers. The patient herself had a stillbirth-abortion sequence followed by a living child.

CASE NO. 75.

Mother died aged 48 of heart disease. Father aged 45 "chest trouble." The patient, an only child, had one abortion and two premature stillbirths before a live child.

Abortion-malformation sequences. A difficulty arises in classifying these cases. They could equally well have been assigned to the other categories already considered, because a foetal malformation is only a late manifestation of various factors which, if they operate earlier in pregnancy, cause an inexplicable abortion. On the other hand, against assigning some of them to the "non-discernible cause" category is the tendency of malformations to recur even if a cause cannot be found. The occurrence of a malformation in a fraternity after a sequence of abortions does in a sense characterize the fraternity, and also, and this point is not without importance, the prognosis is modified thereby. It increases the chances of a subsequent abortion or malformation.

The fact that malformations so often come after a chain of abortions would suggest that the causes of malformations sometimes diminish in intensity with successive pregnancies. Many of the earlier abortions were certainly due to malformations incompatible with intra-uterine life even up to the period of viability. A malformation in a viable child indicates a milder or less profound fault.

ABORTION-MALFORMATION SEQUENCES WITHOUT EVIDENT CAUSE.

No.	Fraternity in Order of Birth
5.	Abortion 14 weeks; meningocele.
10.	Live; stillbirth; stillbirth; premature; abortion; abortion; anencephalous.
21.	Abortion; spina bifida; live; abortion; live; live; live; live.
23A.	Live; abortion; iniencephalous; live.
42.	Spina bifida; abortion; live.
58.	Foetal ascites; abortion; live.
71.	Spina bifida; abortion; abortion; live.

This difficulty in classifying sequences in which a malformation occurred I have met by dividing the group up into two parts, those patients in whom an associated lesion was not present, and those patients associated with some other abnormal condition.

ABORTION-MALFORMATION SEQUENCES ASSOCIATED WITH OTHER FACTORS.

No.	Fraternity in Order of Birth	Associated factor
9.	Live; live; abortion; live; live; abortion; anencephalous	Albuminuria.
29.	Live; meningocele; live; abortion; stillbirth; live; spina bifida	Very poor general health.
52.	Stillbirth; abortion; spina bifida	Poor general health.
76.	Live; live; abortion; anencephalous; live	Poor general health.
7.	Live; live; live; stillbirth; abortion; spina bifida; live; live	Poor general health (Rheumatoid arthritis).
25A.	Live; abortion; iniencephalous; live	Poor general health. Bad family history.
72.	Twins; premature; live; hare lip; abortion; live	Chronic bronchitis.
59.	Abortion; anencephalous; anencephalous	Obesity.
43.	Abortion; anencephalous; anencephalous	Marked masculine secondary sex characters.
66.	Live; premature; anencephalous; stillbirth; abortion	Bad family history.

It will be seen that the associated conditions are similar to those serving to divide the pure abortion sequences into their various categories.

CONCLUSIONS

Abortion sequences and abortion-stillbirth sequences can be divided up into two major groups.

In the first group a cause cannot be found for the sequence of abortions. In this group a spontaneous cure can be expected even without treatment. Most, if not all of these cases, are not instances of true recurrent abortion. They are probably due to the chance incidence in successive pregnancies of the casual abortion-producing factors. If after investigating a case of

sequential abortion an abnormal factor is not found, then there is a good prognosis for a living child.

The second group comprises various categories. The first of these is the "toxaemia of pregnancy, nephritis and hypertension" group. In this group the abortions occur later and the prognosis is not so good, varying with the amount of permanent cardio-renal changes present. Patients with early hypertension carry a bad prognosis even though no other abnormal conditions can be detected. Some of the patients respond well to general treatment, but many disappointments are encountered.

The second category, a small but important one, is that of heart disease. The common mitral lesions do not cause recurrent abortion and in the 3 cases of heart disease in the series there was an associated pulmonary lesion with ensuing peripheral anoxaemia and stasis, which was considered the cause of the recurrent abortions. The prognosis in this group is fair provided adequate rest is obtained.

A third category consists of a heterogeneous group of metabolic and endocrine faults. A rough division of the whole group can be made into those cases characterized by obesity, in which the prognosis is good, and those characterized by poor general condition, often a thyroid lesion and a poor pregnancy response. The prognosis in this sub-group is not good.

Poor family history is a factor commonly found associated with other factors, but in occasional cases it may be the only recognizable abnormality.

The incidence of foetal malformation is closely bound up with the general problem of abortion and abortion-stillbirth sequences, and if a malformation occurs in an abortion-stillbirth sequence for which a cause cannot be found, then the prognosis for a live child is not so good as it otherwise would be.

Appendix

The original theory of the interrelation between casual and recurrent factors in the causation of abortion sequences has been criticized by MacGregor and Stewart, Bacharach, and the Council on Pharmacy and Chemistry of the American Medical Association.

The original theory was based on the experience that about 18 per cent of all pregnancies end in abortion, and assumed that out of this 18 per cent 17 per cent of the abortions were due to

accidental causes and one per cent to recurrent causes. It was considered this partition gave the best correlation with Whitehouse's figures of the numbers of women with 1, 2, 3 and 4 abortions in the population.

The application of this theory to the problem of abortion sequences led to the following conclusions:

1. There is a high spontaneous cure-rate for all abortion sequences.

2. After the occurrence of 3 abortions the probability of a 4th becomes very high, almost amounting to unity. After 3 abortions a truly recurrent cause may be assumed to be present with certainty.

A. MacGregor and Stewart examined the theory, and their criticisms mainly concerned the first of the foregoing conclusions. They consider that a better correlation is obtained if it is assumed that 16 per cent of pregnancies end in abortion from accidental causes, 2 per cent from recurrent causes. By this assumption the chances of a successful pregnancy without treatment following 3 or even 2 abortions are markedly reduced. These authors conclude that the truth may lie between the two assumptions, giving a probability of abortion in a 3rd pregnancy after 2 successive abortions of about 50 per cent, after 3 abortions the probability of abortion in a 4th is 80 per cent, and over 90 per cent after 4 abortions. Thus in a series of cases with at least 2 successive abortions but including a number with 3, the expectation of abortion in the next pregnancy is about 65 per cent. Inclusion into one group of all cases of two or more abortions is valuable because in this way an adequate number of cases are available for study.

B. Bacharach in examining the theory modifies it so as to give a lower spontaneous cure-rate for abortion sequences. His reasons for this modification are that he considers that the one woman who always aborts is outside the chance scheme, and also that in the original scheme the figure of one per cent for the proportion of pregnancies inevitably ending in abortion was too low. He concludes that after 2 or more abortions the expectation of a successful pregnancy is 61.7 per cent, after 3 or more 27.6 per cent and after 4 or more 6.5 per cent. Like MacGregor and Stewart he recognizes the practical need for grouping together cases with 2 or more abortions to provide a group of cases big enough for statistical examination.

C. The author of the "Report of the Council on Pharmacy and Chemistry of the American Medical Association on the value

of Vitamin E Therapy" modifies the original theory quite considerably. His arguments are not too easy to follow except, perhaps, for a professional mathematician but its main steps are as follows:

1. The original argument neglected the fact that the expectation of pregnancy decreases with successive pregnancies. It is very doubtful whether this is strictly true in the particular problem of the woman with 2 or 3 abortions; such a woman, desirous of a live child, usually has her pregnancies very close together.

According to the author such a progressive decrease in the expectation of pregnancy makes it likely that a chance abortion factor is present in 16 per cent of all pregnancies and a recurrent factor in 2 per cent. This accords with MacGregor and Stewart's findings though it is reached by a different argument.

PREDICTED FREQUENCY OF CONSECUTIVE ABORTIONS
(Taken from *Journ. Amer. Med. Assoc.*)

		Number of consecutive abortions					
		1	2	3	4	5	6
Original calculation	F.	0.18	0.0393	0.01501	0.01086	0.0106	0.01003
	R.	0.055	0.254	0.665	0.920	0.945	0.995
	C.	70.2	61.8	27.7	6.5	1.5	
Revised calculation	F.	0.152	0.0450	0.03156	0.02984	0.02963	0.02960
	R.	0.195	0.663	0.940	0.992	0.997	0.999
	C.	70.4	29.6	6.4	0.7	6.2	
Present theory	F.	0.1729	0.06758	0.04685	0.03936	0.03202	0.02780
	R.	0.373	0.813	0.990	0.995	0.999	1.000
	C.	70.9	30.5	16.3	16.2	15.9	

F. Predicted frequency of abortions. R. Proportion of habitual abortions among all abortions. C. Percentage of " spontaneous cure " of women who have had indicated number of consecutive abortions.

For original calculations, $p=0.17$, $p'=1$, $b=0.01$.

For revised calculations, $p=0.126$, $p'=1$, $b=0.0296$.

For present calculations, $p=0.1164$, $p'=0.843$, $b=0.0777$.

2. The original theory assumed that in a small proportion of pregnant women the probability of abortion, p', is equal to 1. A detailed consideration of Whitehouse's original data shows that a better approximation of theory to the data is afforded by the assumption that in 7.8 per cent of all pregnancies there

is a probability of abortion not amounting to unity, but to 0.84 per cent, whereas in the remainder there is a probability of abortion, p′, of 0.116 per cent. These figures give an expectation of pregnancy after one abortion of 86 per cent, after 2 abortions 63.4 per cent, after 3 abortions 45.5 per cent, after 4 abortions 31.5 per cent.

3. The authors then draw attention to the fact that in the case of 4, 5, and 6 abortions the agreement between predicted and actual frequencies is poor. In particular the actual frequency of cases of more than 3 abortions often exceeds the theoretical frequency. This is a very sound criticism. He obviates this by adopting another modification, that the probability of abortion (p′) is somewhat less than unity in a proportion of women (b). In order to calculate p, p′, and b according to this theory, the assumptions were made that the theoretical and observed frequencies of "no abortion" and "one abortion" should agree and that the total expectancy of abortion in every group should be that calculated from theory. On this basis the table on page 79 is drawn up.

The figures of the spontaneous cure-rate—C in the foregoing table—show the contrast between the results obtained between the original theory and the present. In the modified theory the spontaneous cure-rate drops suddenly after 2 abortions to a pretty constant figure of 16 per cent, whereas in the original theory it drops more slowly but progressively. According to either theory there is a tendency for a certain calculable proportion of women to "recover" from repeated abortion.

The author goes on to conclude:

1. The diagnosis of habitual abortion is not justified till a woman has had at least 2 consecutive abortions. This is indicated by the numbers in the rows marked R. These numbers are the ratios of the frequencies of "habitual abortion" to total abortions, and show that after 2 or 3 consecutive abortions nearly all the women in the group are subject to habitual abortion. This confirms an observation of the original paper in which it was stated that all women with 3 or more consecutive abortions might be regarded as a segregated group of truly recurrent aborters.

2. It seems likely that at least 2.8 per cent of pregnant women are liable to repeated abortion and possibly 7.7 per cent are subject to a probability of abortion as great as 0.84 per cent.

3. There is a marked tendency to spontaneous cure of repeated abortion. For example, if a woman has had 2 consecu-

tive abortions the chances are about 1 to 3 that she will not have another.

These various arguments have been set out at length not only for their bearing on the problem of recurrent abortion but as illustrating a technique for sorting out random from recurrent causes in any morbid condition having a compound aetiology.

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Vaginal Calculus

BY

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A VAGINAL CALCULUS is of rare occurrence and references to it in the literature are scanty. Such cases have been recorded by Brayne[1] and Farquhar Murray,[2] while Taby[3] reports 12 other examples. The case I record brings the number up to 15. This case is unique in being an example of vaginal calculus complicating parturition.

In the older literature, more frequent reference to the occurrence of vaginal calculi was found, owing to the fact that the operation of colpocleisis was then in vogue for the relief of vesico-vaginal fistulae.

Aetiology. The calculi usually form in the vagina but on occasions may reach that site by ulceration of a bladder stone through the vesico-vaginal septum. Two conditions must be present for their formation: a congenital or acquired vaginal stricture and the occurrence of urinary leakage into the vagina through a fistula or as the result of urinary incontinence. Subjects of vaginal calculi fall roughly into two age groups: that of childhood and adolescence, in which the responsible factors appear to be congenital stricture of the vagina and urinary incontinence, and those of later life in which urinary fistulae and post-traumatic vaginal strictures play the aetiological role.

Size. The calculi vary in size from that of a millet seed up to 4 inches in diameter; the largest yet recorded. The larger stones are usually single.

Composition. Occasionally a foreign body such as a suture, swab or a thermometer bulb forms the nucleus of the stone, but the bulk is derived from the deposition of urinary salts. Analysis of these calculi has shown the presence of urates, oxalates, phosphates, carbonates, uric acid, but the phosphatic type naturally predominates, as they form in an inflammatory alkaline medium.

Treatment. This naturally involves cure of the vaginal stric-

ture and removal of the calculus, which has, on occasions, required fragmentation before it could be extracted. At a later date, it would be necessary to deal with a urinary fistula or overcome urinary incontinence.

Case Report. Mrs. N. H., aged 25 years. A primigravida at term. Early in pregnancy, she had noted some slight urinary incontinence but otherwise had been in excellent health. Labour commenced spontaneously on 9th June, 1940, and was characterized by weak and infrequent pains. She was examined on 11th June, 1940, by the midwife, who found the cervix to be dilated to the size of a crown piece and presenting a hard mass on the left side; this she scraped off and extracted. It proved to be a vaginal calculus measuring $1\frac{1}{2}$ by $\frac{3}{4}$ by $\frac{3}{4}$ inches and was composed of a central nucleus of blood pigments surrounded by a grey cortex of phosphates and carbonates. This unusual finding caused the midwife to summon medical aid and I was called to the case by the patient's doctor.

Despite 48 hours in labour, both mother and the foetus were in excellent condition. The so-called cervix proved to be a vaginal septum situated half-way up the canal and presenting two circular apertures lying in the transverse axis. It was evident that the calculus had occupied the foramen on the left side. I was unable to reach the cervix satisfactorily *per vaginam*, but on rectal examination it was quite easy to palpate the vertex and outline the half dilated cervix.

Mrs. N. H. was transferred to the East Suffolk and Ipswich Hospital, where I administered a low spinal anaesthetic and divided the septum by two postero-lateral incisions. After recovery from the anaesthesia, sedatives and oestrin were administered and full dilatation of the cervix awaited. At 4 p.m. on June 12, 1940, after some 80 hours in labour, the 2nd stage was reached. A second spinal anaesthetic was administered and a lateral episiotomy performed, after which the foetus was manually rotated to the anterior position and the forceps applied. As soon as the head descended on to the perineum, the foetal heart ceased to be audible. A stillborn child, with a lumbar spina bifida and bilateral talipes equino-varus, was extracted, but its death was due to the snapping of an abnormally short and fragile cord close to the umbilicus. A normal 3rd stage of labour followed and the episiotomy was repaired.

The day after delivery, urine was detected escaping *per vaginam*, so a self-retaining catheter was inserted into the bladder in order to provide continuous drainage. Despite this

untoward event, an afebrile puerperium followed. After discharge from hospital, the patient was kept under observation in the out-patient clinic. A post-natal examination revealed a normally involuted anteverted uterus, while a slight semilunar prominence on the posterior vaginal wall marked the site of the septum: anteriorly a tiny vesico-vaginal fistula could be seen.

In order to keep the patient comfortable, the bladder, from the time of delivery onwards, was drained continuously by a self-retaining catheter, into a rubber urinal strapped to the thigh. Three months later the patient was asked to re-enter hospital for a surgical repair of the fistula, but she wrote to say that she was by that time free from any urinary leakage and would not come.

Summary

The literature on vaginal calculus is reviewed and the aetiology and pathology discussed. An additional case is reported.

References

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2. Farquhar Murray, E. "A vaginal calculus," *Brit. Med. Journ.*, Feb. 6, 1926.
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WILLIAM FORDYCE

Obituary

William Fordyce

WILLIAM FORDYCE died on November 6th at the little town of Tillicoultry at the foot of the Ochil Hills, whither he had gone from Edinburgh in the summer of 1940 in search of quiet and freedom from war's alarms. It is good to know that he found what he sought, and that his death was as peaceful as the falling of a leaf on a still autumn day.

Although born in Liverpool in 1863, Fordyce came of Fife parents and lived all his early life in that county, so that he inherited and acquired all the local patriotism associated with the natives of "the Kingdom." After leaving school at Anstruther, he studied at St. Andrews University where he took his Arts degree. He then came to Edinburgh University, and after a particularly distinguished undergraduate course, graduated M.B., C.M., with first-class honours, in 1888. Five years later he proceeded to the degree of M.D., and in 1898 he was elected a Fellow of the Royal College of Physicians of Edinburgh.

His great admiration for Professor Sir Alexander Simpson and close friendship with Simpson's brother-in-law, Dr. Freeland Barbour, led Fordyce to follow in the same lines of work, and for some years he acted as assistant to Simpson in both his University and private work. Subsequently he started lecturing in the "Extra-mural School," as was the wont in Edinburgh in those days of all young aspirants to consulting rank. In due course he was appointed to the staff of the Royal Maternity and Simpson Memorial Hospital, and later to the Gynaecological Staff of the Royal Infirmary. He also acted for many years as Gynaecologist to Leith Hospital and to the Hospital for Diseases of Women in Archibald Place.

During those years of his most active professional work Fordyce was a popular younger member of a group of men whose work and skill in midwifery and gynaecology brought great distinction to the Edinburgh Medical School—Sir Alexander Russell Simpson, Sir John Halliday Croom, Drs. Freeland Barbour, Berry Hart, Milne Murray, F. W. N. Haultain, J. W. Ballantyne,

Haig Ferguson and Lamond Lackie. With his death the last link with that great generation of specialists is severed.

Fordyce was a brilliant diagnostician and a neat and dexterous operator. In midwifery his small hands, as well as the skill with which he could use them, were the envy of many of his colleagues. His diagnostic skill was often seen at its best in connexion with tubal pregnancy, and he explained this to the writer by saying that he thought extra-uterine pregnancy was commoner than was usually supposed, and that in any doubtful case he "plumped for it," and more often than not was right. In his operating he often deplored the fact that he had never had the advantage of the thorough training as house-surgeon in a surgical charge, which is now so wisely insisted upon by the Royal College of Obstetricians and Gynaecologists as an essential preliminary to specializing. As a result of this, as well as of a deeply rooted modesty, he tended to exaggerate his operative limitations, but within his self-imposed limits he was a complete master. In much the same way modesty kept his professional writings within a comparatively small compass, and most of his papers dealt with cases of exceptional interest which seemed to him to demand being recorded. Among his papers were several on ectopic gestation, and two or three on pregnancy in malformed uteri; while he also described cases of concealed accidental haemorrhage associated with eclampsia, rupture of the uterus following the use of pituitrin to induce labour, and one of the earliest cases of hysterectomy under spinal anaesthesia. All of these were contributed to the Edinburgh Obstetrical Society, of which at the time of his death he was one of the oldest Fellows. His interventions in the Society's discussions were always positive and to the point and were usually illustrated from his wide practical experience. In 1919 he was elected President of the Society and his address on that occasion was an interesting historical review of the development of gynaecological surgery.

In 1929 Fordyce became one of the Foundation Fellows of the now Royal College of Obstetricians and Gynaecologists.

As a teacher Fordyce was deservedly popular. He spoke with great simplicity, clearness and humour, never becoming ponderous or pontifical, but rather speaking to his students as if they were colleagues of equal standing.

Among his many gifts was that of writing verse, and it was here and in his social life that his personality found its freest expression. Most of his verses were light and topical, but all were irradiated by his keen sense of humour, and not infrequently by the true spirit of poetry. Many of them dealt with his favourite

sports of fishing, golf and curling. Undoubtedly his happiest days were those which he spent in salmon fishing on the lochs at Morar and Altnashellach, and he returned to them again and again in his verses. Such original verses are very apt to be lost to posterity, but fortunately Fordyce was persuaded some 6 years ago to make a collection of what he thought to be the best of them and publish it privately. This small volume, *The Old Sport and Other Verses*, will serve to recall many a happy evening to his friends.

His broad humanity of spirit and his humour made Fordyce an eminently clubbable man, as all the older members of the Gynaecological Visiting Society will remember. And the same gifts made him for many years a particularly welcome guest at medical and other dinners at which his recitations of his own verses were a source of the most delightful postprandial entertainment. He occasionally delighted in poking fun at a colleague in his verses, and during the recitation the blushing victim sat in a state of delicious trepidation waiting for the "leg pull" which, when it came, was always gentle and painless, and was as much enjoyed by him as by the rest of the audience. Among the clubs in which he will be most missed are the Aesculapian Society and the Medico-Chirurgical Club—Edinburgh's two oldest medical dining clubs—the Monks of St. Giles, a select literary and social coterie in which he was known and loved as Father Profundus, and the Scottish Arts Club.

Fordyce retired from active practice some dozen years ago, and during these latter years of retirement he became more and more of an invalid. But his gift of friendship never waned, his humour kept its old freshness, and even his skill in versifying did not forsake him.

R.W.J.

We deplore the loss of one of the medical notabilities of Edinburgh in the person of Dr. William Fordyce, whose death will be felt not only by his medical colleagues, but also by his many literary and artistic friends. Fordyce was indeed a personality, and was as well known outside the medical circle in Edinburgh as within it as an excellent and witty after-dinner speaker and a poet of no mean ability. On these counts, as well as for his own personality, he was *persona grata* at many important functions, and was a much-sought-after guest at the many Edinburgh University reunion dinners held in other cities in Great Britain. His recitations and songs were always greatly appreciated, and seldom, if

ever, was he left in peace until he had recounted the vagaries of the dog Tige, a silver statuette of which he presented to the Residency at the Royal Infirmary, Edinburgh, on his retiral from the active staff. His poems were varied, but the majority were either about his favourite sport, fishing, or had a medical flavour. One, "The Oracle," was published in many papers in this country and abroad during the last war on account of its cleverness and topicality. It was a great delight to all his immediate friends to receive as a Christmas present some years ago a bound copy of his poems, and this book is a priceless possession now. As a Monk of St. Giles, an old Edinburgh literary society, and as a member of the Aesculapian and Medico-Chirurgical Clubs his gifts were fully appreciated.

Fordyce had many other interests: in fact, there was little going on about which he was not cognisant. He was a great sportsman, a good golfer, and a canny curler, but his main forte was fishing, and he was never so happy as when he was on holiday at Achnashellach catching salmon.

In these remarks it might appear that his surgical and obstetrical prowess had been forgotten, but they have been ably recorded by another and it only remains for me to say that he seemed to have an especial flair for diagnosis, and that extra-uterine gestation to him was like the partridge to the pointer: he seemed to have an uncanny knack of diagnosing such cases when least expected. His lectures were most unusual, and never an hour passed without his relating some amusing anecdote to stress an important point: he was at his happiest in teaching when the class laughed the most. Certainly his students could never forget the important facts he so amusingly illustrated. Who, after hearing Fordyce, could undertake a decapitation without remembering the difficulties of the operation so ably illustrated by his misspent day in the Cowgate?

Professionally, his first love was his Gynaecological Ward at the Infirmary, and he always preferred his work there to his work in private practice. Many of his poorest patients not only benefited from his medical and surgical skill, but also received untold kindness which helped them in their domestic lives. His obstetric work did not give him quite the same pleasure and this was principally due to his hatred of seeing anyone in pain, a hatred which was accentuated as he grew older: even the salutary pains of labour filled him with a certain degree of abhorrence, and he was never really happy until the labour was safely over and all pains had ceased.

Shortly after Fordyce's retiral from the active staff of the Infirmary, 13 years ago, he began to suffer from symptoms which might be attributed to some disturbance of the semi-circular canals and he was unable to enjoy his leisure as fully as he had anticipated. His ardour for fishing, however, continued unabated, and it was with great delight that just before the war, having been practically confined to his house for several years previously, he caught at Achnashellach a 27-pound salmon, which was one of the biggest ever caught in the district.

Fordyce felt the war deeply and it was a great regret that he evacuated himself to Tillicoultry over a year ago and cut himself off almost entirely from his large circle of friends. His loss is already keenly felt and will be more so when the piping times of peace arrive and the many social functions he adorned are resumed.

W.F.T.H.

Review of Current Literature

Director: FREDERICK ROQUES, M.A., M.D., M.Chir. (Cantab.), F.R.C.S., F.R.C.O.G.

THIS Review contains the lists of contents and abstracts of the more important articles from the journals with which the *Journal of Obstetrics and Gynaecology of the British Empire* exchanges.

The Review of Current Literature has kept the readers of the Journal in touch with current literature throughout the world; owing to the war many journals with which the *Journal of Obstetrics and Gynaecology* previously exchanged are no longer received. At the end of the year an Index of all the subjects contained in the articles of the journals reviewed is printed. Arrangements are also made to include abstracts of important articles on border-line subjects, such as Physiology, Biology, and Biochemistry.

LIST OF ABSTRACTORS

J. LYLE CAMERON, F.R.C.S.; W. E. CROWTHER, M.B.; R. H. B. ADAMSON, M.D.; B. JEAFFRESON, F.R.C.S.; P. MALPAS, F.R.C.S.; T. N. A. JEFFCOATE, F.R.C.S.; MEAVE KENNY, F.R.C.S.; JANE H. FILSHILL.

The British Medical Journal

August 30th, 1941.

*A case of puerperal tetanus. Bruce Maclean and P. Challen.

*Persistent lactation with a note on Chiari's and Frommel's disease. Barton Gilbert.

September 6th, 1941.

The midwifery of a general practice (*B.M.J. Supplement*). R. A. Ratcliff.

*Fragarine: an inhibitor of uterine action. Sir Beckwith Whitehouse.

September 27th, 1941.

*Treatment of haemorrhagic disease of the newborn. A. I. S. Macpherson.

October 11th, 1941.

A new sulphonamide (*sulphonamide E.O.S.*). N. Mutch.

Melanotic carcinoma: sudden spread after hysterectomy. L. J. Temple.

October 18th, 1941.

*Thrombosis in the superior longitudinal sinus following childbirth. J. Purdon Martin.

Radiographs and disproportion. J. V. O'Sullivan and F. M. Crawshaw.

October 25th, 1941.

*Volvulus of the caecum, associated with putrid puerperal endometritis, and gangrenous vulvitis. Isaac Rose.

November 8th, 1941.

*The problem of operation for retroverted uterus. Coralie Rendle-Short.

A Case of Puerperal Tetanus.

The patient was admitted 15 days after forceps delivery and perineal suture. She had had stiffness of the jaw for 5 days and gradually developed typical spasm of the masseter muscles. Tetanus organisms could not be found in the stools or vaginal swabs.

She was treated by isolation in a dark room, large doses of anti-tetanic serum intravenously, and also by sulphonamide and sulphapyridine. To ensure periods of rest, evipan was given intravenously, and avertin *per rectum*. Chloral hydrate was also helpful. She made a complete recovery and was free from muscle spasm by the fourteenth day after admission.

It is assumed that the infection arose in the lacerated vaginal tissue, the organisms possibly gaining entrance from the rectum.

Persistent Lactation with a Note on Chiari's and Frommel's Disease.

The literature is mostly concerned with the association of persistent lactation and utero-ovarian atrophy. The syndrome is sometimes known as Frommel's disease, but Chiari had described it previously.

Persistent lactation may be independent of genital atrophy and menstruation does not necessarily return when lactation ceases. The occurrence of amenorrhoea depends on the degree of atrophy.

The case described is of a woman, aged 35, who had had one child 16 years previously. She had lactated continuously since weaning the child one year after its birth. Menstruation was regular, but the uterus felt small on examination. There was no other evidence of pituitary disturbance. The patient thought it was normal to lactate persistently after childbirth, and admitted expressing milk from the breasts each day.

The author concludes that the case is not typical of Frommel's and Chiari's disease since there was very little utero-ovarian atrophy. Manipulation of the breasts by the patient may have played a part in maintaining the secretion of milk.

Fragarine: An Inhibitor of Uterine Action.

An infusion of raspberry leaves is used by country folk for allaying the pain of labour and menstruation. Investigations by Professor J. H. Burn show that such infusions when administered to a spinal cat produce a relaxa-

tion of the uterus, and also an initial fall in blood-pressure followed by a rise in blood-pressure. The uterus did not relax if the suprarenal glands were excluded and hypogastric nerves divided.

The active principle of raspberry leaves has not been isolated, but the name *fragarine* is suggested.

Infusions were administered to patients during the puerperium, and the uterine reaction tested by Chassar Moir's intra-uterine bag technique. The effect is to cause a relaxation of the uterine muscle, the contractions being diminished in force and frequency. There is a slight fall in systolic blood-pressure, but no subsequent rise as in test animals.

Further investigations may show that fragarine will be useful in the treatment of irregular uterine action in labour.

TREATMENT OF HAEMORRHAGIC DISEASE OF THE NEWBORN.

An attempt was made to evaluate the relative merits of intramuscular injections of blood, blood-transfusion, and vitamin K in the treatment of haemorrhagic disease.

Three cases were treated by intramuscular injections of whole blood, and in only one was the course of the haemorrhagic disease arrested.

Two cases were treated by blood-transfusion. There was a rapid improvement in the prothrombin level, and cessation of haemorrhage. But there was a subsequent rapid fall in the prothrombin level.

Six cases were treated by vitamin K analogues. In all, the bleeding was controlled within two hours, and there was a rapid and permanent rise in the prothrombin level. Deep intramuscular injections are as effective as intravenous administrations. Vitamin K was also given successfully to three other cases in which haemotherapy failed, and to a further three cases the details of which are not given.

Two cases of erythroblastosis foetalis which showed spontaneous haemorrhage were also treated successfully with vitamin K.

The author concludes that vitamin K analogues are much the best in treatment, but in cases of serious blood loss it would be advantageous to combine this treatment with blood-transfusion.

THROMBOSIS IN THE SUPERIOR LONGITUDINAL SINUS FOLLOWING CHILDBIRTH.

This condition has long been known to exist, but is rarely described in recent English literature. The diagnosis depends on, (*a*) signs of raised intracranial pressure due to interference in the absorption of cerebrospinal fluid from the longitudinal sinus; (*b*) signs of obstruction of the superior cerebral veins. This may or may not result in thrombosis in these veins. If it does, it produces paralysis according to the part of the brain affected, and this may be preceded by convulsions. Convulsions are less likely when venous thrombosis is secondary to obstruction in the sinus, than when it is primary.

Not all cases are diagnosed, and a large thrombus may exist in the sinus without giving rise to symptoms.

Three cases are described one of which terminated fatally, but the death

of the patient is ascribed to a lesion in the spinal cord rather than the cerebral condition.

If the patient is free from gross heart disease or hypertension, venous thrombosis is the most probable cause of haemiplegia occurring during the puerperium. Both groups of symptoms need not be present since sinous thrombosis and venous thrombosis may occur independently.

Treatment consists in allaying convulsions by luminal, reducing intracranial pressure by intravenous injections of 50 per cent glucose, or repeated lumbar puncture. Extension of thrombosis could be prevented by heparin.

This condition is rare except in association with childbearing, and is not related to the nature of the delivery. There is often evidence of thrombosis elsewhere in the body, and it is probable that it arises as a result of emboli from thrombosed pelvic veins. These emboli reach the brain through the vertebral plexus of veins—the anatomical connexions having been recently described by Batson. To avoid this complication, any patient suspected of having pelvic thrombosis should be nursed in the sitting position, and abdominal binders and straining at stool should be avoided.

VOLVULUS OF THE CAECUM, ASSOCIATED WITH PUTRID PUERPERAL ENDOMETRITIS, AND GANGRENOUS VULVITIS.

A primigravida of 38 was admitted 17 hours after a difficult forceps delivery. She was extremely ill with rapid feeble pulse and some abdominal distension. The edge of a complete perineal tear was black and gangrenous. She was treated with anti-gas-gangrene serum and sulphanilamide, and decompression of the distended bowel by a duodenal tube. Her condition did not improve, so after plasma transfusion the peritoneal cavity was drained through a small incision, on the basis of a diagnosis of peritonitis. The patient died the following day, and post-mortem examination revealed a volvulus of the caecum.

The history of the case suggested that the volvulus probably occurred four days before delivery.

THE PROBLEM OF OPERATION FOR RETROVERTED UTERUS.

This paper deals with 120 patients operated on for retroversion; 92 of them were re-examined three to seven years after operation. The technique employed was shortening of the round ligaments combined with dilatation of the cervix and curettage: 50 per cent were cured anatomically and symptomatically; 29 per cent showed a good anatomical result but still had symptoms, and 8 per cent were cured of symptoms although the retroversion was found to have recurred. In 11 patients the operation was a complete failure both from the point of view of the anatomical result and the relief of symptoms. Twenty-one patients became pregnant after the operation, and the uterine displacement recurred in 4 of these. Of 19 patients who originally complained of sterility, 11 became pregnant after the operation.

The author advises trial of a pessary before operation is carried out, and considers that the operation offers a reasonable hope of cure of sterility when no other causal factor can be found.

T. N. A. JEFFCOATE.

The Medical Journal of Australia

July 26th, 1941.

*Pulmonary tuberculosis and pregnancy. H. B. Oxenham.

August 23rd, 1941.

*On the nature of eclampsia. W. J. Penfold.

September 20th, 1941.

*A case of primary peritoneal pregnancy. C. Williams.

PULMONARY TUBERCULOSIS AND PREGNANCY.

Oxenham, who is a clinical assistant in the Anti-tuberculosis Clinic of the Royal Prince Alfred Hospital, Sydney, gives a short review of the writings on this subject by tuberculosis specialists during the years 1929 to 1938, and in addition refers to De Lee in the *Year Book of Obstetrics and Gynaecology* for 1936.

Quoting Ornstein and Kovnat, Castlen, Schultze-Rhonhof, Krause, Jennings, Mariette, Litzenberg and Bogen and drawing upon his own clinical experience the writer is inclined to take a somewhat optimistic view of the tuberculous patient and pregnancy. He considers that the tuberculosis sanatorium should have a maternity ward directly attached, so that pregnant patients can be treated throughout by experts during pregnancy, labour and the puerperium.

He asks for routine tuberculin tests to be made on all antenatal patients and that all reactors should be radiologically examined. He considers that if this were generally done the proportion of tuberculous patients among the maternity cases would be similar to that in the general population and, further, that detection of disease would be carried out in time for useful treatment to be undertaken.

He considers that greater government financial help is needed for the care of dependants while treatment is being carried out.

He considers that very few cases of tuberculosis call for therapeutic abortion but he insists that all tuberculous pregnant women should be kept under close observation by a tuberculosis specialist. He pleads for the shortening of the second stage of labour by the administration of the barbiturates, nitrous oxide, and oxygen when necessary. He would keep the patient at rest for at least three weeks after delivery and forbid breast feeding to minimize the chances of a flare-up of the disease.

Where there is an open lesion he would remove the infant from the neighbourhood of the mother entirely.

ON THE NATURE OF ECLAMPSIA.

Penfold writing from the bacteriological point of view concludes that eclampsia is an acute sarcolactic acid intoxication occasioned by a large production of this substance within the body and by an interruption of its disposal by the synthesis of glycogen, which depends upon the presence of some

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infection. Working from this conclusion he advocates the following preventive treatment:

(1) Isolate the patient for some days before her confinement.

(2) Determine the presence of any defective cardiac compensation or other cause of defective oxygen supply to the tissues as the synthesis of lactic acid to glycogen is aerobic.

(3) Try to prevent any emotional disturbance.

(4) Determine the existence of twin pregnancy and if possible test the power of the patient to get rid of lactic acid.

(5) Classify the patient according to her capacity to get rid of lactic acid from the blood.

As regards the treatment of an established case of eclampsia the writer would rely entirely upon the estimation of the defect in alkali reserve by Van Slyke's method, the calculation of the total blood-volume, followed by the administration of a sufficient quantity of alkali intravenously to bring the alkali reserve to normal.

He does not appear to believe that treatment as laid down by Strogonoff, or by the Dublin School, is of any value.

A Case of Primary Peritoneal Pregnancy.

Clive Williams records the history of a patient who was operated on as an emergency case with the diagnosis of ruptured tubal pregnancy. There had been a period of 14 days of amenorrhoea in a single woman of 23 years, who had taken various drugs to terminate her amenorrhoea.

At the time of her admission she was in a collapsed condition which called for a preliminary glucose-saline transfusion before any operative treatment could be attempted.

On opening the abdomen both Fallopian tubes and ovaries were found to be intact and nowhere showed any sign of pregnancy. The abdomen was full of blood and fresh bright blood was welling up from the pouch of Douglas in an alarming amount. On clearing out the blood and clot a foetus of about 4 weeks' pregnancy was delivered from the pouch of Douglas; an area to the left of the mid-line on the floor of the pouch was found to be bleeding, chorionic tissue was still attached to it.

The chorionic tissue was rapidly stripped away and an area about one inch in diameter was found to be eroded; at the anterior border of this area a large artery was bleeding profusely. This artery appeared to be the cervical branch of the left uterine artery. The anterior surface of the rectum was also eroded over an area of about one centimetre in diameter.

The bleeding vessel was clamped and ligatured and the eroded surfaces were peritonized. The patient was hurriedly returned to bed in fair condition; she recovered.

The patient's condition did not allow of a leisured detailed study of her pelvis and, as she recovered, no further examination could be made. The gestation sac was bounded by the floor of the pouch of Douglas, the anterior surface of the rectum and the left ovary.

R. H. B. Adamson.

The Journal of the American Medical Association

Vol. cxvi, No. 24, June 14th, 1941.

*Preparation and transfusion of safe universal blood. E. Witelsky, N. Klendshoj, and P. Swanson.

*The adrenogenital syndrome. O. Wintersteiner.

*Hormone assays. S. C. Freed.

Vol. cxvi, No. 25, June 21st, 1941.

*Artificial insemination. F. Seymour and A. Koesner.

Vol. cxvi, No. 26, June 28th, 1941.

Heparin as a prophylactic against thrombosis. C. Crafoord and E. Jorpes.

PREPARATION AND TRANSFUSION OF SAFE UNIVERSAL BLOOD.

The object of the paper is to show how universal blood can be rendered safe for emergency transfusions. The accidents which do occasionally happen with this blood are attributable to a high titre of the iso-agglutinins anti-A (α) and anti-B (β) in the plasma of the donor. Normally the administered blood is diluted sufficiently to make these anti-agglutinins of negligible effect, but when they are present in high titre in the donor's blood reactions may occur.

The authors recommend that the anti-agglutinins α and β shall be neutralized by the addition to the donor's blood of the group specific substances A and B. Substance A can be isolated from commercial pepsin, peptone and mucin. Substance B can be isolated from the gastric juice of human beings belonging to blood-group B. Both substances are similar carbohydrate-like compounds and are also similar to the complex carbohydrates which are recognized as the bearers of the type specificity of pneumococci and other organisms.

Universal blood conditioned by the addition of substances A and B can be given to any patient independently of the patient's blood-group and, in emergencies, even without cross grouping.

THE ADRENOGENITAL SYNDROME.

Wintersteiner reviews the adrenogenital syndrome and its hormonal and chemical basis. The fundamental premise of the work of Vines, Broster and their co-workers that the adrenal can elaborate both androgens and oestrogens appears to be well established now by chemical research. The chemistry of the steroid metabolism of the adrenal cortex is summarized in the paper. As regards androgens there is some agreement on the point that malignant cortical tumours are often associated with high levels of excretion regardless of the sex of the patient and the type of symptoms. Exceptions, however, do occur. As regards oestrogens, abnormally high amounts seem to be excreted sometimes in virilism with or without adrenal tumours, but more often in those cases of adrenal tumours classed as instances of Cushing's syndrome.

It would appear reasonably certain that some part of the androgens excreted by normal subjects are derived from an extragonadal source and as far as present knowledge goes this can only be adrenal cortex. The presence

of residual oestrogenic substances in the urine of male and female castrates invites a similar explanation. In this regard crystalline oestrin (theelin) has been isolated from beef glands.

With regard to the actual importance of the normal adrenal cortex in the regulation of sex functions the evidence is not conclusive and the experimental results reveal rather a potential availability than an active functional secretion of androgens and oestrogens from the adrenal cortex. The biochemist might be tempted to take the more limited view that these substances are the incidental by-products of cortical steroid metabolism, which, to judge from the number of compounds isolated from the gland, most of them physiologically inactive, seem to be very complex.

HORMONE ASSAYS.

This is a very thorough review of the recorded investigations on the excretion of hormones in normal and pathological states. The paper is too detailed to allow of abstraction but the author's final statement may be quoted, "Physicians will be disappointed if they expect simple or casual hormone assays to furnish significant information except in a few isolated cases. Intensive and carefully controlled investigations are essential in contributing to knowledge of normal or abnormal endocrine physiology."

Of particular interest are those parts of the paper which deal with the hormonal urinary excretion in abortion and the toxaemias of pregnancy.

ARTIFICIAL INSEMINATION.

The National Research Foundation for Eugenic Alleviation of Sterility, Inc., circularized 30,000 doctors who might have used artificial insemination: 7,642 replies were received, bearing witness that 9,489 women had become pregnant by this method. Donors were used in one-third of the cases. The proportion of boys to girls resulting was roughly 8 to 5 with the husband's semen, 7 to 5 when a donor was used. The incidence of ectopic pregnancy was only one-sixth of the normal incidence. The incidence of abortions was only one-fifth of the normal rate. There was a negligible incidence of stillbirths and no instance of any foetal abnormality. In 45 per cent of the successful pregnancies 12 inseminations were given.

(No comment or discussion is given on the reasons for the very low incidence of the normal accidents of pregnancy in the series, and the results seem to evade some of the laws of probability.)

PERCY MALPAS.

REPORTS OF SOCIETIES

THE ROYAL ACADEMY OF MEDICINE IN IRELAND

A meeting of the Section of Obstetrics of the Royal Academy of Medicine in Ireland was held in the Royal College of Physicians on Friday, October 17th, 1941; the President of the Academy, Mr. Seton Pringle, was in the chair.

Dr. N. FALKINER read his presidential address on the subject of

PLACENTAL INFARCTS.

He alluded to the generally accepted teaching with regard to these lesions and to the fact that most teachers in obstetrics did not attach much significance to their association with the toxaemias of pregnancy.

Dr. N. Falkiner next described the work that Young had published in 1914. The main points in this work were the accurate description of the red infarct and its association with eclampsia. Professor Young had evolved an attractive hypothesis and had made a most valuable contribution, which included many interesting and stimulating statements, with regard to placental anatomy and physiology.

Recently workers in America had revived the views put forward by Professor Young. Among these were Bartholomew and his co-workers. Careful examination of placentae from all toxaemic cases had resulted in the recognition of certain types of placental infarct in association with different clinical manifestations. Among the conclusions reached by these workers were: (1) Placental infarcts of the more acute types were definitely associated with the toxaemias of pregnancy. (2) It was possible to predict the type of infarct to be found in the placenta from a knowledge of the history. (3) With the experience of examining placentae as *unknowns*, it had been found possible to establish criteria for an exact classification of placental infarcts and their relation to toxaemia.

Bartholomew had evolved hypotheses with regard to the effects of hypocholesterolemia and hypothyroidism. With regard to the significance of hypocholesterolemia and hypothyroidism as predisposing to infarcts in the placenta, the opinions of both Young and Bartholomew coincided in that they believed that the acute placental infarct has an aetiological significance. They differ in their interpretation of the causal factors in producing these lesions.

Dr. Falkiner showed sections from twenty cases of toxaemia of pregnancy and demonstrated the constant occurrence of acute infarcts in pre-eclampsia and eclampsia and that the older or more chronic infarcts are associated with nephritic toxaemias.

Dr. GIBBON FITZGIBBON thanked the President for his excellent address and said that he, himself, had done no investigations on this subject. He had found a few infarcts and had more or less discounted them as being causative elements in the toxaemias of pregnancy.

Dr. BETHEL SOLOMONS said that the amount of work shown by the display of placentae this evening was extraordinarily interesting; but, alas, it brought little new light on the problem of the toxaemias. However, the work was valuable inasmuch as it might prove to be a link in the chain in the elucidation of the problem.

It would be of great value if a series of placentae from normal cases was compared with a series of placentae from toxaemic cases.

He enquired if post-mortems had been done on the cases in which the uterus had been removed with the placenta *in situ*, for this examination might shed new light on the decidual circulation; the relation of infarcts, and a good or bad decidual circulation, to toxaemias was still an unsolved puzzle. The general belief was that when infarcts were present with good decidual circulation the toxaemia was more severe.

The Master of the National Maternity Hospital, in thanking the President for his excellent and most interesting paper, and the many beautiful slides, referred to the very great delicacy of the vessels in the placenta, and said that the rate of growth of these vessels was enormous. When growth of this kind occurred something was bound to go wrong, and this would explain to some extent the development of infarcts. The most interesting question in his opinion was whether the toxaemia was due to the infarct, or the infarct due to the toxaemia. He thought that the infarct was due to the toxaemia. In cases of chronic nephritis and vascular hypertension it was not unreasonable to expect that when there were new blood-vessels in the placenta the condition there would be more marked. The toxaemia was bound to have an effect on the placenta.

Professor A. H. DAVIDSON said that Dr. Falkiner was one of the first really scientific presidents that the Section had had for some time. They had heard from him that night an excellent and most instructive paper. He (Dr. Davidson) did not know a great deal about the question of infarcts. He thought the chief question was, did infarction come from the maternal circulation or from the foetal circulation? In his opinion it came from the latter. During his time as Master of the Rotunda Hospital a number of babies born of toxaemic mothers had had albuminuria; a fact which rather suggested that they had nephritis.

Dr. R. M. CORBET said he joined the other speakers in hearty congratulations to Dr. Falkiner on his extremely able and beautifully presented communication.

He knew very little about placental infarction, but he had been greatly impressed with the researches of Bartholomew and his co-workers.

While Dr. Falkiner did not suggest that these infarcts were aetiologically significant, Bartholomew was strongly of the opinion that they were the cause of the toxaemia. If this were so, it raised certain speculations. To have the foetal vessels primarily affected would postulate a hypercholesterolemia in the

foetal circulation, also the question might be raised why the foetus is not always affected to the same degree as the mother.

Dr. Falkiner suggested that, when the infarction is acute, the whole cotyledon is involved. If this were so, the toxins liberated may not be absorbed by that cotyledon, but would be carried upwards in the maternal blood-stream, to the sub-chorionic pool, where there is little or no absorption, and from thence into the general circulation, where they may be taken up by the maternal tissues before the blood returns to the placenta, hence leaving the foetus unaffected.

Again he would like to congratulate Dr. Falkiner on the excellence of his work.

Dr. O'DONEL BROWNE asked Dr. Falkiner were there any changes in hyperemesis gravidarum which would be at all comparable with those in eclampsia? In patients in whom pregnancy was quite normal, did he regard albuminuria as *post* or *propter hoc* in cases of placental lesions?

Dr. J. S. QUIN said that this paper of Dr. Falkiner must be looked upon as being only a very very early progress report. He thought the question was, were these lesions the cause or the effect of the toxaemia? If they were the cause, then the case of toxaemia from severe accidental haemorrhage which Dr. Falkiner had mentioned must surely demand another explanation. In regard to the question of the maternal or foetal origin of the condition Dr. Falkiner considered that both the maternal and the foetal circulations were involved. How did the separation of the placenta in these cases compare with the appearance of the infarcted areas in a recent infarction?

Dr. W. R. F. COLLIS in thanking Dr. Falkiner for his very interesting and stimulating paper said that it was especially interesting from the point of view of foetal death and immature birth which were the largest causes of foetal mortality. His experience was that in every case in which there was toxaemia in the mother there was toxaemia in the baby as well. Wherever the toxin was it certainly got into the foetal circulation. He asked Dr. Falkiner if he had considered what was the cause of the actual thrombosis. What was the mechanism of it? Was it foetal or maternal? Had any work been done on the blood coagulation of babies born of eclamptic mothers?

Dr. J. G. GALLAGER asked if any work had been done in connexion with the circulation on the vessels of the living foetus. What was the rule of the inter-foetal contractions on the circulation?

Dr. Falkiner, in replying, said that this work was still going on. The decidua had not been examined in any case. It was a most difficult thing to examine the decidua in the placental circulation. There were reasons to back up the view that disturbance of the maternal circulation would cause infarction. The greater proportion of patients, who had sugar in the urine during pregnancy, developed albuminuria. He had not yet sectioned any placentae from cases of placenta praevia. It was very important in these cases to understand the circulation.